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Editorial

Acute suppression of urine

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The term *urinary suppression* has an old-fashioned ring. Today, terms more indicative of scientific erudition have succeeded one another—hemoglobinuric nephrosis, lower nephron nephrosis, acute tubular necrosis, acute renal failure, and the like—regardless of whether they possess anatomic or physiologic validity. We have used the term *acute suppression of urine* as a title not only because scanty or no urine is the essence of our subject matter but also because this is the observed clinical phenomenon.

Urinary suppression does not imply renal disease. It can occur in the presence of entirely normal kidneys if the renal blood flow is sufficiently reduced or if the outflow of urine is obstructed. In either situation—inadequate inflow of blood or inadequate outflow of urine—prompt recognition and appropriate treatment not only cures the urinary suppression but prevents the renal damage which is so prone to follow prolonged renal ischemia or obstruction of the urinary tract.

Although circulatory collapse (shock) is the most common cause of renal ischemia, it must be remembered that the systemic arterial pressure need not be excessively low. Renal vasoconstriction may virtually deprive the kidneys of blood and yet, by diverting the usually large proportion of cardiac output from the kidneys, serve to sustain the circulation elsewhere.

Obstruction at the neck of the bladder or below is easily recognized. Not so, however, that which simultaneously, or more often successively, blocks first one and then the other ureter. Unless the cause of urinary suppression is crystal clear, ureteral catheterization to establish patency is obligatory.

The intrarenal causes of acute urinary suppression cannot be cured, for the most part, by the active intervention of the physician, as can those causes due to impaired inflow or outflow. However, the majority of lesions are reversible if the patient can be kept alive and in a reasonable state of health for a long enough time. Since irreversibility is rarely predictable, a hopeful attitude is always in order.

Little is to be gained by listing the innumerable causes of intrinsic acute renal failure save to note that specific measures as well as general ones may be indicated. In acute poststreptococcal glomerulonephritis, penicillin therapy may be in order. Although probably too late to be of much usefulness once urinary suppression from mercury poisoning has occurred, dimercaprol (BAL) should be employed. In pyelonephritis, and particularly that variety known as acute papillary necrosis, the offending organism must be isolated, appropriate antibacterial therapy instituted, and the precipitating urinary tract obstruction and/or diabetes treated. It is, of course, paramount that every endeavor be

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made to prevent circulatory collapse and to combat it vigorously once it has occurred.

Although renal ischemia or nephrotoxins probably account for the majority of cases of intrinsic acute renal failure, the fact remains that in about one third of the cases no single cause can be determined with assurance. Nor do we know why one individual may suffer from severe oligemic shock with no subsequent renal damage, whereas another person whose hypotension has been of minimal severity and duration develops renal failure.

Once it has been ascertained that the urinary suppression cannot be cured by improving the circulation or removing an obstruction, the problem then is that of combating the physiologic consequences of renal failure which result largely from the loss of two important renal functions: the function of maintaining a relatively constant volume and electrolyte composition of the extracellular fluid, and the function of removing certain products of catabolism which are no longer required by the body. In acute renal failure these tasks devolve upon the physician. The first of these presents no difficulty. By assiduous control of what is allowed to enter the body the volume of the extracellular fluid may be maintained constant and its composition stable save for the accumulation of the products of catabolism. The intake of water should equal the measured losses through any channels plus the difference between insensible loss and insensible gain. The former, for a 70-kilogram adult, resting, afebrile in a temperate environment, is about 800 ml. evaporated from skin and lungs. The latter amounts to about 400 ml. derived from catabolism and preformed cell water. Thus, the daily water requirement is the measured loss plus about 400 ml. Since the estimate of insensible loss and gain is at best an approximation, the most satisfactory guide of water balance is careful daily weighing of the patient. A daily loss of 200 to 300 Gm. (from the catabolism of body tissue) is indicative of a reasonably satisfactory fluid balance. The severely oliguric or anuric patient will obviously lose no appreciable sodium in urine. However, extrarenal losses—emesis, diarrhea, drainage—should be replaced quantitatively.

Since the end products of fat and carbohydrate metabolism consist chiefly of carbon dioxide and water in amounts readily disposed of by the lungs, it is largely products of protein metabolism—sulfate, phosphate, hydrogen ion, potassium, magnesium, and nitrogenous moieties—which accumulate during urinary suppression, and which can be minimized by reducing protein catabolism to as low a level as possible. Although acidosis is to be expected as a chemical finding in acute renal failure, it seldom presents clinical manifestations. Similarly, the hypocalcemia which accompanies the rising levels of serum phosphate rarely leads to tetany, nor does elevation of serum magnesium often present a clinical problem.

The accumulation of potassium in the extracellular fluid, however, constitutes a real problem, since fatal cardiac arrhythmias result from sufficient elevation of the concentration of potassium in the serum. For readers of this Journal it is unnecessary to detail the sequence of electrocardiographic changes which ensue as the concentration of potassium in the extracellular fluid rises, nor to emphasize that the electrocardiogram, rather than the actual level of potassium, serves as the best indicator of impending catastrophe.

Of the nitrogenous moieties of protein catabolism, urea constitutes the quantitatively largest fraction. However, there is little evidence that urea at the highest concentrations encountered clinically is directly responsible for any symptoms in man,[1] and, in fact, it is stated that patients show clinical improvement after dialyses against a urea content of the bath which is sufficiently high to prevent lowering of their blood urea concentration.[2]

Although urea itself appears to be nontoxic, when its concentration in the serum rises, there is a similar elevation in its concentration within the lumen of the gastrointestinal tract, where there are enzymes capable of forming ammonia from urea. A local irritant effect of this ammonia has been held responsible for the anorexia, nausea, and emesis which may be encountered in uremia,[1] and a systemic effect appears implicated in patients with azotemia and liver disease who apparently cannot readily reconvert ammonia formed thus

in the gastrointestinal tract to urea, and who may develop confusion and coma associated with an elevated concentration of ammonia in the blood.[3] It should also be mentioned that the bacteria in the gastrointestinal tract are capable of forming free phenolic derivatives[4] from the aromatic amino acids—tyrosine, phenylalanine, and tryptophane—which may adversely affect the nervous system. Blood guanidine (and derivatives) become elevated in renal failure. In dogs, injections of guanidine cause gastrointestinal disorders and muscular twitching.[5] However, the amounts used experimentally were far above any ever encountered in terminal uremia in man. Although high concentrations of both creatinine and urate are encountered, there is no evidence that they lead to the production of symptoms. Other nitrogenous moieties which result from protein catabolism or gastrointestinal bacterial degradation of nitrogenous substances have not been sufficiently studied to warrant discussion.

The desired diminution in protein catabolism is accomplished in two ways: no exogenous protein is administered; endogenous catabolism is reduced by affording a constant supply of glucose and by maintaining complete rest. The regimen then for the management of the patient with uncomplicated acute renal failure is most simple: (1) complete rest; (2) water in an amount so that body weight decreases daily by about 200 or 300 grams; (3) dextrose in a minimal amount of 100 Gm. daily, given in divided doses throughout the 24 hours; (4) sodium given only to replace losses; (5) avoidance of any other intake, and particular caution in the administration of medications, including antibiotics, which are usually eliminated in the urine, and which may accumulate in the patient with oliguria.

With such a regimen, the patient with *uncomplicated* renal failure rarely presents any but minor manifestations of "uremia" despite elevation of the serum nonprotein nitrogen to 200 to 300 mg./100 ml., and the onset of diuresis is seldom delayed beyond 10 days if the intrinsic renal lesion is due to a nephrotoxin. I have seen such cases due to ingestion of mercuric chloride, inhalation of carbon tetrachloride, sensitivity to sulfonamides, and the ingestion of unknown nephrotoxins. The mortality in such *uncomplicated* acute renal failure is virtually nil—but, unfortunately, the number of such *uncomplicated* cases is also small. The would-be suicide is prone to ingest sufficient mercuric chloride so that severe hemorrhagic enterocolitis results, and the victim of carbon tetrachloride has often ingested or inhaled an amount that destroys his liver long before urinary suppression becomes a limiting factor for his existence. By and large, acute renal failure occurs in the setting of antecedent disease, major surgical or accidental trauma, or combinations of these. Thus, of 100 cases analyzed by Bluemle, Webster and Elkinton[6] (75 of these patients were sent to the Hospital of the University of Pennsylvania after an average period of oliguria of 1 week), only 9 were due to nephrotoxins. Four of these cases were uncomplicated and the patients survived. Three of the deaths after inhalation of carbon tetrachloride were ascribed to hepatic necrosis, and the 2 deaths after mercury poisoning resulted from infection secondary to the gastrointestinal lesion rather than to the renal disorder. Of 38 cases which developed after operation or other trauma, death ensued in 28.

Similar data may be noted in the report of Shackman, Milne and Struthers[7] of patients transferred to the Hammersmith Hospital in London for treatment of acute renal failure. Death occurred in 42 of 50 "surgical" cases and in 22 of 29 cases of post-traumatic oliguric renal failure.

Teschan and his associates, of the Renal Branch of the U.S. Army Surgical Research Unit at Fort Sam Houston, Texas,[8] report 160 fatalities in 242 "post-traumatic" cases (both surgical and accidental trauma are included) collected by the Study Group on Acute Renal Failure. The source of the patients is not given, but presumably many were transferred from local hospitals to renal centers.

Frightening as the above figures are, it must be borne in mind that they have been collected from renal units and for the most part represent referred cases, patients who were considered by the originating institution as likely to require specialized treatment. No doubt, many

patients with milder and briefer episodes of urinary suppression were treated and recovered at the local level of hospitalization. Over the past 9 years, during which approximately 18,000 major surgical operations have been performed in my hospital, there has been only one case of acute tubular necrosis consequent to such operation in which the renal lesion was the important contributory cause of death—death on the seventh day due to pulmonary edema from fluid overloading.

This is not intended to minimize the alarming mortality encountered among patients with severe post-traumatic or postsurgical acute renal failure, such as are admitted to specialized renal centers. This mortality is found despite rather free use of external dialysis employed to correct electrolyte abnormalities or clinical manifestations associated with the "uremic" state, and appears to be associated with poor wound healing and sepsis. Teschan and his associates[8] particularly note that these "complications" are conspicuous in the patients who develop oliguric renal failure but relatively rare in patients subjected to similar surgical or accidental trauma who do not develop urinary supression. They believe that these may not be "complications" at all but rather manifestations of the damaging influence of the "uremic state" on recuperative or homeostatic processes and physiologic defense mechanisms.

I cannot comment on the phenomenon of poor wound healing, since I have not seen severe postsurgical or traumatic cases. In the nephrotoxic group, I have not been impressed with any undue susceptibility to infection other than might be expected, particularly where there has been instrumentation of the urinary tract. Furthermore, I am not aware of an undue prevalence of infection in patients who are suffering from chronic uremia, despite the fact that these individuals are anemic, often are undernourished because of anorexia and vomiting, frequently suffer from chronic acidosis, and may exhibit a tendency to bleed, nor am I aware of reports of undue susceptibility to infection. In a recent study of *terminal* pneumonia contributory to the death of the patient, Kneeland and Price[9] found no higher incidence in renal disease than in malignancy, brain disease, or congestive heart failure.

Nonetheless, the mortality in the postsurgical and traumatic cases of severe oliguric renal failure is such that Teschan's suggestion of "prophylactic" dialysis to prevent the "uremic" state deserves careful consideration. Whether this procedure will be of value cannot be determined a priori on theoretical grounds. Only a carefully controlled clinical appraisal will furnish the desired information. In the meantime, dialytic treatment seems to be indicated for patients who fall in one of two groups.

The first group includes those whose level of serum potassium and electrocardiogram suggest that a serious arrhythmia is in the immediate offing. The indication for dialysis (in order to lower serum potassium) in this group seems absolute. Temporary measures, such as the intravenous infusion of dextrose and insulin or the administration of sodium bicarbonate, should be employed to lower serum potassium in situations in which a life-threatening arrhythmia seems imminent, only until some other means of eliminating potassium from the body can be readied.

However, when time is not of the essence and cardiac catastrophe is not anticipated within hours, there is now available a method of lowering serum potassium and of maintaining it at a normal level. Carboxylic cation-exchange resins capable of removing potassium from the gastrointestinal secretions have been available for a decade.[10] However, their large mesh size made them unpalatable in general, and particularly for the uremic patient with a propensity for nausea and emesis. Furthermore, they tended to form conglomerate masses in the stool which often led to fecal impaction. A new sodium-exchange resin (Kayexalate, Winthrop Laboratories, New York City) has the consistence of a powder which can be suspended in a small volume of water and ingested without difficulty; it has a theoretical binding capacity of 3.1 milliequivalents per gram of resin, and, in practice, has been found to exchange about 1 milliequivalent of potassium per gram.[11] Combined with the administration of 10 to 20 ml. of a 70 per cent sorbitol syrup every few hours until

modest diarrhea was produced, a dose of 15 Gm. of the resin given four times daily was uniformly effective in causing a gradual lowering of the levels of serum potassium in a group of severely oliguric patients.[11] Rectal administration was also found to be effective. Once the level of potassium in the serum became normal, 5 Gm. of resin four times daily was sufficient to prevent subsequent elevation.

The second group for whom dialytic treatment may be indicated includes patients who are doing poorly and have "uremic" symptoms. It is worth stressing, however, that the signs and symptoms of "uremia" may be difficult to distinguish from those of anoxia, hypercapnia, sepsis, or liver disease. Merrill and others who have had a large experience with hemodialysis are fairly unanimous in the opinion that such treatment results in a generally improved status which may allow the patient to tolerate other complications more successfully. However, in the absence of properly controlled studies of morbidity and mortality with and without hemodialysis, we cannot comment on the utility of the procedure save in cases of life-endangering hyperkalemia.

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Clinical communications

What is Fallot's tetralogy?

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The classic association of morbid anatomic features described by Fallot,[1] in 1888, and usually accepted as constituting the tetralogy which bears his name, comprise pulmonary stenosis or atresia, ventricular septal defect, overriding aorta, and hypertrophy of the right ventricle. But there is a wide range of both morbid anatomy and symptomatology among patients whose hearts possess a ventricular septal defect and pulmonary stenosis, and there is a difference of opinion about what constitutes Fallot's tetralogy. Furthermore, the hemodynamic errors which result are imperfectly understood.

One point of confusion is whether or not the term *Fallot's tetralogy* implies that there is cyanosis, or, at least, that there is arterial oxygen unsaturation. Patients are sometimes divided into those who are cyanotic and those who are not. I prefer that the term should be confined to patients who exhibit desaturation of the arterial blood, despite the fact that progressive pulmonary stenosis may occur and may result in the development of cyanosis in a patient who was previously not cyanotic. It is best used to describe patients who have pulmonary stenosis and a ventricular septal defect with a right-to-left (reversed) shunt. The several features of Fallot's tetralogy will be discussed, and an attempt will be made to define the condition and to relate it to certain other conditions.

Hypertrophy of the right ventricle. Hypertrophy of the right ventricle merely indicates that this chamber is subject to strain. It seems inexpedient to include this feature as part of the complex of anomalies which constitute Fallot's tetralogy. It is no more a part of the picture of this condition than it is of many others which impose a strain upon the right ventricle.

Dextroposition of the aorta. Dextroposition of the aorta, with overriding of both ventricles, is usually considered to be an essential feature of Fallot's tetralogy,[2 (p.399), 3 (p.110), 4 (p.183)] and its degree is believed by many to be an important factor in determining the amount of cyanosis[5-7] by causing the aorta to receive some blood directly from the right ventricle.[3 (pp.111 and 117)] Keith, Rowe, and Vlad,[2 (p.428)] however, state that some of their most severely anoxic infants have had only moderate overriding of the aorta.

An examination of the evidence casts serious doubts on the importance of aortic override in producing hemodynamic errors in Fallot's tetralogy. The degree of override found is extremely variable[2 (p.399), 3 (p.110), 5, 6, 8]; it may be absent in a few patients who otherwise appear to have typical tetralogy,[9] and it may be present in patients who have a ventricular septal defect but no pulmonary stenosis, as in the Eisenmenger complex. The anatomic studies of Selzer[5] and Selzer and Laqueur[6] have shown that, whereas varying degrees of aortic override, from inappreciable to major, can occur in Fallot's tetralogy, the recognition of the milder degrees is difficult when there is a large defect of the membranous septum, even on direct examination. All who have

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studied hearts at postmortem examination would agree with this observation. Dextroposition of the aorta is, thus, an unreliable index of Fallot's tetralogy.

There is good evidence to prove that overriding of the aorta is unimportant in the causation of cyanosis due to a right-to-left shunt. The relief of pulmonary stenosis by closed infundibular resection or pulmonary valvotomy by the technique of Brock[10,11] may relieve cyanosis completely and convert the right-to-left interventricular shunt into one which is entirely from left to right,[7,12] despite the fact that the aorta is still overriding. A similar condition follows the open repair of Fallot's tetralogy if the pulmonary stenosis is eliminated but the ventricular septal defect is imperfectly closed, and this may lead to death.[9]

Additional evidence of the functional unimportance of dextroposition of the aorta is provided by cases of "atypical" Fallot's tetralogy. Rowe, Vlad, and Keith[13] report four such cases in which a ventricular septal defect combined with pulmonary stenosis was associated with a large left-to-right shunt, normal arterial oxygen saturation, and systemic systolic pressures in the right ventricle. Aortic override was thought to be present in all four of these patients. In three of them a catheter entered the aorta from the right ventricle; the right ventricular pressure pulses were of normal pattern in the two in whom they could be satisfactorily analyzed; the aorta arched to the right side in one of them, and in the one who came to autopsy (not the one with a right aortic arch) a considerable degree of aortic override was found. Keith, Rowe, and Vlad[2] have added a fifth patient to these four, and this patient also had an aortic arch on the right side. An aortic arch on the right side is rarely associated with simple ventricular septal defect or pulmonary stenosis with normal aortic root. Keith[14] found only one example in 400 patients with ventricular septal defects, and Campbell[15] found only one among 75 patients with simple pulmonary stenosis. Rowe, Vlad, and Keith[13] found no example of such an association among 100 patients.

The evidence, therefore, is that the degree of aortic override in Fallot's tetralogy is extremely variable, that its recognition, at least in the milder degrees, is not easy, and that it has little influence upon the direction of shunts or the severity of cyanosis. In this latter respect, Fallot's tetralogy resembles Eisenmenger's complex. Eisenmenger[16] himself maintained that overriding of the aorta was of little functional importance in the complex which he described, and the evidence in favor of this much-debated opinion has recently been ably marshaled by Wood.[17] Dextroposition may, however, have some embryologic significance for it occurs in about 20 per cent of the cases of Fallot's tetralogy and in a similar proportion of cases of the Eisenmenger complex. It also occurs commonly in transposition of the great vessels and in persistent truncus arteriosus. These are all conditions associated with large ventricular septal defects of the nonrestrictive type (*vide infra*) and/or anomalous septation of the truncus arteriosus and bulbus cordis. Both Selzer[5] and Warden and associates,[18] however, point out that the override may be partly acquired after birth as the result of disproportionate flow of blood through the aorta and the pulmonary artery. Eisenmenger[16] demonstrated that the aorta is normally located in such a relation to the ventricular septum that, if the membranous portion of the latter is deficient, it comes in contact with both ventricles, so that overriding of the aorta is a by-product of a large ventricular septal defect and not a developmental dextroposition.

The ventricular septal defect. The combination of a ventricular septal defect of a critical size with pulmonary stenosis of a critical degree of severity is the essence of Fallot's tetralogy. The writer has classified interventricular and aortopulmonary communications into nonrestrictive and restrictive varieties and has given an account of the hemodynamic upsets to which they give rise.[19] A nonrestrictive defect is one which neither restricts the flow of blood nor occasions a pressure gradient. The resistance to flow through such a communication is not greater, and may be much less, than that afforded by the normal pathways. In the case of a ventricular septal defect this is so when the diameter

of the orifice equals or exceeds that of the aortic ring,[20,21] but the definition is a hemodynamic and not an anatomic one. A restrictive defect is smaller than this, so that it offers a higher resistance to flow than does the normal pathway, and it occasions a pressure gradient between the chambers or vessels which it connects.

A nonrestrictive ventricular septal defect will insure that the pressure in the two ventricles will be identical throughout the cardiac cycle under all conditions. Furthermore, throughout the ejection phase, the pressure in the aorta and pulmonary artery will be the same as that in the ventricles, provided that there is no obstruction to outflow from either ventricle. If pulmonary or aortic stenosis is present, the pressure in the vessel beyond the obstruction will, of course, fall. In Fallot's tetralogy the pressure in the two ventricles is, in fact, the same throughout the cardiac cycle, and their systolic pressures are identical with that in the aorta,[2 (p.413), 9, 13] because the ventricular septal defect is always of the nonrestrictive type. Additional proof of this reasoning is afforded by the fact that, after relief of the pulmonary stenosis by infundibular resection or pulmonary valvotomy, the pressures in the two ventricles and in the aorta (during systole) remain identical, even though relief of the stenosis is sufficient to cause a large left-to-right shunt, with pulmonary flows two or more times greater than systemic flows, oxygen saturations in the arterial blood of 95 per cent or more, and pulmonary arterial systolic pressures of up to 60 mm. Hg.[12] These findings prove that in Fallot's tetralogy the equality of pressures in the two ventricles is due entirely to the nonrestrictive nature of the interventricular communication and is independent of the pulmonary stenosis.

In Fallot's tetralogy the ventricular septal defect is nonrestrictive functionally and large anatomically; it varies between 1 and 3 cm. in diameter.[2 (p.399), 6, 9, 18] In Eisenmenger's complex, also, the defect usually measures between 1 and 3 cm. in diameter,[6,17] whereas in uncomplicated ventricular septal defect it is more often less than 1 cm. across.[6] Kirklin and associates[9] define Fallot's tetralogy as "a congenital cardiac malformation with ventricular septal defect of a size approximating the aortic orifice and pulmonary stenosis of such severity that it, in combination with the ventricular septal defect, results in identical right and left ventricular pressures." I would disagree with this definition, in that I do not believe that the pulmonary stenosis plays any part in maintaining equality of pressures in the two ventricles.

Because the ventricular septal defect is nonrestrictive in Fallot's tetralogy, the pressure pulses recorded from the two ventricles are identical and of normal pattern, with an ejection phase plateau. This distinguishes Fallot's tetralogy from pulmonary stenosis with normal aortic root, in which condition Bouchard and Cornu[22] have shown that there is a typical and abnormal right ventricular pressure pulse. This displays delayed ascent during isometric contraction, absence of the ejection phase plateau, and delayed fall in pressure, resulting in a symmetrical, pointed tracing which is strikingly different from the left ventricular tracing from the same patient. Rowe, Vlad, and Keith[13] found the abnormal type of curve in two patients with simple pulmonary stenosis plus a ventricular septal defect, so that the combination of the two anomalies need not affect the characteristic curve found in simple pulmonary stenosis. In such cases the septal defect is small and restrictive.

The characteristic feature of the ventricular septal defect in Fallot's tetralogy, therefore, is that it is nonrestrictive, and this ensures equality of pressure in the two ventricles at all times, under all conditions, and irrespective of the presence and degree of pulmonary stenosis.

Pulmonary stenosis. Pulmonary stenosis is as fundamental a feature of Fallot's tetralogy as is a nonrestrictive ventricular septal defect. The stenosis usually occurs in the infundibulum, where it may be high, intermediate, or low,[11] but it may be at the pulmonary valve, or affect both sites. Rarely, it occurs in the pulmonary trunk[23]; the writer has seen one such case. Fallot[1] classified pulmonary stenosis and atresia combined with dextroposition of the aorta as a single anomaly. Although, pathologically, atresia represents the ulti-

mate in stenosis, hemodynamically it profoundly alters the course of the blood supply to the lungs,[3 (p.110)] which is by way of the aorta, and, thence, the bronchial arteries and the ductus arteriosus. The prognosis of this condition is much more grave, and it is better classified under a separate heading.

Although pulmonary stenosis (or atresia) plays no part in maintaining equality of pressure in the two ventricles, it does account for two important features of Fallot's tetralogy, namely, the right-to-left interventricular shunt and the reduced pressure and flow in the pulmonary artery and its branches.

The severity of the pulmonary stenosis is critical, for, if the resistance which it imposes on the flow of blood exceeds the systemic vascular resistance, then the shunt between the ventricles will be from right to left, whereas if it is less than this, the shunt will be in the opposite direction. When the two resistances are approximately the same, the shunt will be balanced or bidirectional.

A relative increase in severity of pulmonary stenosis with age may cause shunt reversal, and so convert a patient who is not cyanotic into one who is cyanotic. It is easy to relate "atypical" cases of Fallot's tetralogy, with clinical and physiologic shunts from left to right,[7,13] to the classic variety with cyanosis. It is simply a matter of whether the pulmonary stenosis offers more or less obstruction to flow than does the systemic peripheral vascular resistance.

Alterations in the balance between these two resistances readily explain the marked alterations in the degree of cyanosis which may occur rapidly in children with Fallot's tetralogy, and the attacks of cyanosis to which they are liable, especially between the ages of 6 and 18 months.[24] These may be caused either by a transient increase in the severity of stenosis or by a decrease in the systemic peripheral vascular resistance.

Hamilton, Winslow, and Hamilton[25] demonstrated a decrease in peripheral vascular resistance in one patient, and this mechanism forms a ready explanation of the relationship of attacks of cyanosis to hot weather and infections which was noted by Keith, Rowe, and Vlad,[2 (p.401)] but which they ascribed to loss of extracellular water, with deleterious changes in the already abnormal ratio of cell volume to plasma. Wood[26] showed that the administration of amyl nitrite produced an increase of cyanosis and of arterial oxygen unsaturation, with a fall in the mean and pulse pressure in the pulmonary artery which accompanied the fall in systemic blood pressure.

On the other hand, Wood[26] also demonstrated that, in five patients with Fallot's tetralogy, spontaneous attacks of cyanosis, with or without syncope, were caused by an increased resistance in the pulmonary outflow tract, and that the blood pressure did not fall in any of these patients. Functional infundibular stenosis operates in this manner whether the organic stenosis is valvar or infundibular. When consciousness is lost, arterial oxygen unsaturation becomes extreme, the pulmonary arterial pressure becomes very low, the murmur disappears, and a state of functional pulmonary atresia is established.[26,27]

Wood[26] believes that the spontaneous attacks of cyanosis which occur in Fallot's tetralogy are due to functional infundibular stenosis, which explains their relief by morphine or cyclopropane, and concluded with confidence that "peripheral vasodilatation is not the cause of these attacks." This, however, is probably not invariably so, and it cannot explain attacks which occur in patients who have organic pulmonary atresia.

Definition of Fallot's tetralogy. From the foregoing analysis, I conclude that the fundamental feature of cyanosis in Fallot's tetralogy is the combination of a nonrestrictive ventricular septal defect with pulmonary stenosis of such degree that it imposes a resistance to the flow of blood which is greater than that caused by the systemic peripheral vascular resistance. Overriding of a dextroposed aorta, although usually present, is of little importance hemodynamically, but it may have embryologic significance. Hypertrophy of the right ventricle should not be named as part of an abnormal developmental complex.

Fallot's tetralogy may conveniently be defined as pulmonary stenosis with re-

versed or bidirectional shunt through a nonrestrictive ventricular septal defect. The term *Fallot's tetralogy* is a misnomer, for there are only three developmental defects, and one of these is unimportant functionally and extremely variable in degree anatomically. If an eponymous title is still desirable, to honor him who described the condition so well, even though he was not the first to do so,[28-32] and because of its brevity, then the term *Fallot's anomaly* would be more appropriate.

The definition suggested above is functional rather than anatomic. It excludes patients with left-to-right shunts who are not cyanotic, but allows that the only difference is in the severity of the pulmonary stenosis. There is a close analogy between the conditions discussed in this paper, on the one hand, and those characterized by interventricular or aortopulmonary communications without pulmonary stenosis, on the other. When the pulmonary vascular resistance is low, the shunt is from left to right, but, when it reaches and then exceeds the systemic vascular resistance, the shunt becomes balanced or bidirectional, and then reversed. Eisenmenger's syndrome results, and, if the shunt is an interventricular one, the condition is called *Eisenmenger's complex*. The fundamental difference between Fallot's anomaly and Eisenmenger's complex is that in the former the obstruction to pulmonary flow is in the region of the pulmonary infundibulum or valve, whereas in the latter it is in the region of the small pulmonary muscular arteries. The definition of Fallot's anomaly given here is in line with that suggested for Eisenmenger's complex by Wood,[17] namely, "pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over 800 dynes sec./cm.$^{-5}$), with reversed or bidirectional shunt through a large ventricular septal defect (1.5 to 3 cm. across)." Communications between the two circulations which produce the Eisenmenger reaction are nearly always of the nonrestrictive variety when they occur at the ventricular or aortopulmonary level.

Summary

The essence of Fallot's tetralogy is the combination of a nonrestrictive ventricular septal defect with pulmonary stenosis of sufficient severity to impose a resistance to flow greater than that of the systemic peripheral vascular resistance.

The nonrestrictive ventricular septal defect ensures that the pressure in the two ventricles is identical throughout the cardiac cycle under all conditions, and that their pressure is the same as that in the aorta throughout the ejection phase. The pulmonary stenosis reduces the pressure and flow in the pulmonary artery, and is responsible for a bidirectional or right-to-left shunt between the ventricles.

Overriding of the aorta is quite variable in degree anatomically, and of little importance hemodynamically. Right ventricular hypertrophy is a nonspecific reaction to stress.

Fallot's tetralogy is defined as pulmonary stenosis with a bidirectional or reversed shunt through a nonrestrictive ventricular septal defect.

The term *Fallot's tetralogy* is a misnomer. A more desirable eponymous title would be *Fallot's anomaly*.

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The electrocardiogram in the presence of myocardial infarction and intraventricular block of the left bundle-branch block type†

A clinical pathologic study

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The electrocardiographic identification of myocardial infarction in the presence of left bundle-branch block has been reported to be difficult[3,14,16] or impossible.[14] Yet this electrocardiographic diagnosis is of importance inasmuch as left bundle-branch block is often a complication of myocardial infarction; it was present in 20 (7.7 per cent) of 375 cases of acute occlusion of the coronary artery reviewed by Master and associates.[10] The investigation reported herein was undertaken to provide additional data on the nature and significance of findings encountered when complexes of the left bundle-branch block type had been recorded in patients proved to have myocardial infarction at the time of necropsy.

Review of selected literature

Sodeman and associates[13] in 1944 stated: "When the septum is extensively damaged, the electrical forces produced by its activation are reduced or abolished, and the initial negativity of the right ventricular cavity is transmitted to the left, and, consequently, to those regions on the left side of the body that are initially positive in left branch block when the septal muscle is healthy. When this happens, Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also. . . ." Several cases have been reported to support this theory.[2,3,12,14,16]

A Q wave in the leads facing the left ventricle could be caused by normal left-to-right activation of the ventricular septum if the block causing the prolonged QRS complex were very low in the septum or were in the free wall of the left ventricle.[6,11] At times it is difficult to distinguish left bundle-branch block due to block in the septum from so-called peri-infarction block. Grant and Dodge[6] have

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proposed criteria for making this distinction.

An unusual electrocardiographic position of the heart may be attended by Q waves in Leads I and aV_L and in leads over the left ventricle. Sodeman and associates[13] noted that a Q wave in Lead I could result if the free wall of the right ventricle faced the right arm. This often occurs in the vertically placed heart in the dog.[13] Lapin and Sprague,[8] in 1948, reported on a patient with left bundle-branch block who had Q waves in Leads I and aV_L and in leads from the left precordium on inspiration only.

Chapman and Pearce,[2] in 1957, described several cases of anteroseptal infarction in the presence of left bundle-branch block with an rsR′ configuration in Lead V_6. They thought that the downward deflection could be called a " 'delayed Q wave,' delayed by the time necessary for passage of the wave of activation through the septum before it reaches the infarcted area." In some cases the downward deflection did not reach the base line, resulting in an R wave with an early deep notch.

Myers and associates[11] believed that Q waves may be present over the right ventricle in the presence of left bundle-branch block but without infarction, because the right-to-left activation of the septum may produce a greater negative force over the right ventricle than the positive force produced by the free wall of the right ventricle. They concluded: "Thus, in cases of left bundle branch block, the presence or absence of septal infarction cannot be determined from the contour of the QRS complex in right ventricular leads."

Cabrera and Friedland,[1] in 1953, suggested that "A notch with a duration of .05 sec. or more, observed in the terminal portion of QRS in the precordial leads that show a morphology rS or Qs (usually V_3 and V_4)," is a sign of anteroseptal infarction in the presence of complete left bundle-branch block.

A Q wave in Lead III was present in 10 of 28 cases of left bundle-branch block without clinical evidence of infarction reported by Dressler and associates,[3] but they stated: "We have never observed a Q wave in Lead II when left bundle-branch block was uncomplicated." They concluded that "Q waves or W-shaped QRS complexes (or Q wave equivalents) in Lead II" are "suggestive of posterior infarction in the presence of left bundle branch block."

Kennamer and Prinzmetal,[7] in 1956, concluded: "In patients with bundle branch block, the development of myocardial infarcts involving large amounts of subepicardial muscle may be manifest by a decrease in the magnitude of the R wave in precordial leads overlying the left ventricle or aV_F."

Wilson and associates,[15] referring to infarction in the presence of left bundle-branch block, stated: "Displacement of the RS-T segment and changes in the T wave may occur if the area of the QRS complex is small. When the area of the QRS complex is large, the alterations in the T complex due to infarction are likely to be obscured by those produced by the conduction defect." Experimental infarcts in dogs in the presence of left bundle-branch block have resulted in elevation of the S-T segment over the site of the infarct, as shown by Kennamer and Prinzmetal.[7]

Definition of terms

"Left bundle-branch block" is an electrocardiographic diagnosis, as used in this paper. It does not indicate the site of the disturbance in conduction or the cause. Cases were included in this study if they met all of the following criteria: (1) QRS complex of 0.12 second or greater, (2) sinus origin of the QRS complex, (3) P-R interval of 0.12 second or greater, (4) no S wave in Lead I, (5) broad R wave in left precordial leads, or in Lead aV_L if the left precordial leads were transitional in form, (6) intrinsicoid deflection starting 0.08 second or longer after the beginning of the QRS complex in leads over the left ventricle, and (7) QS or rS wave forms in Lead V_1 with normal intrinsicoid deflection. The disturbance in conduction in some of the cases may not have been in the septum but peripherally in the left ventricle.[2,6,11]

Infarcts were called large when they involved, in one continuous area, more than one fourth of the circumference of the left ventricle in two of the five slices excluding the first (apical) slice. Infarcts of the ventricular septum were called large if the

infarct was transseptal, and if more than one half of the septum was involved in two of the five slices excluding the apical slice. Transmural and transseptal infarcts not extensive enough to be called large were called small. Infarcts which occurred 6 weeks or less before the death of the patient were called recent.

Material and method

Cases in which necropsy was performed at the Mayo Clinic between January, 1947, and April, 1959, and in which all of the following characteristics prevailed were selected for this study: (1) a confluent myocardial infarct, either recent or healed, as revealed on examination, (2) availability of electrocardiograms, including a minimum of the three standard leads and three precordial leads, taken at a time when the infarct was present as judged retrospectively by pathologic examination correlated with clinical findings, and (3) presence of left bundle-branch block when the infarct was present as judged by pathologic examination and clinical history. Thirty-nine cases met these criteria. In all cases the heart weighed more than would be expected for the height, body weight, and sex of the patient; the mean increase was 100 per cent.

The methods of study and description of the heart in this laboratory have been reported by Edwards.[5] The following were examined to determine the position, extent, and age of the infarct: (1) the preserved heart in all but one case, (2) photographs taken at the time of necropsy, and (3) histologic sections taken from the site of the infarct and from all other quadrants of the left ventricle, including the septum. The ages of the recent infarcts were estimated on a histologic basis according to the criteria of Mallory and associates,[9] and

Table I. *Incidence of certain electrocardiographic changes according to location and size of infarct**

Infarct		*Incidence of indicated electrocardiographic change*†				
Location	*Size*	*Q wave in Lead I*	*Q wave in Lead* aV_L	*Q wave or Q-wave equivalent in Lead* V_6	*R wave in Leads* V_{3-4} *smaller than in Leads* V_{1-2}	*Late notch in S wave in Leads* V_{3-4}
Anteroseptal	Large	8/13	9/12	9/12	10/13	9/12
	Small	0/10	3/8	0/8	2/10	2/8
Lateral	Large	1/3	1/3	1/3	0/3	0/3
	Small	0/2	1/1	0/1	1/2	0/1
Posterior	Large	1/2	1/2	1/2	0/2	1/2
	Small	0/6	0/5	0/5	0/6	0/5
Posteroseptal	Large	0/1	0/1	1/1	0/1	0/1
	Small	0/3	1/2	0/2	0/3	0/2
Circumferential subendocardial	Large	0/1	0/1	0/1	0/1	1/1
Anterior subendocardial	Large	0/1	0/1	0/1	0/1	0/1
Total number of infarcts		10/42	16/36	12/36	13/42	13/36
Total number of cases		8/39	14/33	9/33	13/39	12/33

*All large infarcts and the largest infarct in cases in which there was no large infarct are represented in the table.
†Incidence is expressed as the ratio of the number of infarcts associated with a given electrocardiographic change to the number of infarcts observed for association with that change. For example, the 8/13 in the first column signifies that a Q wave was present in 8 of 13 instances in which both Lead I was recorded and a large anteroseptal infarct was present.

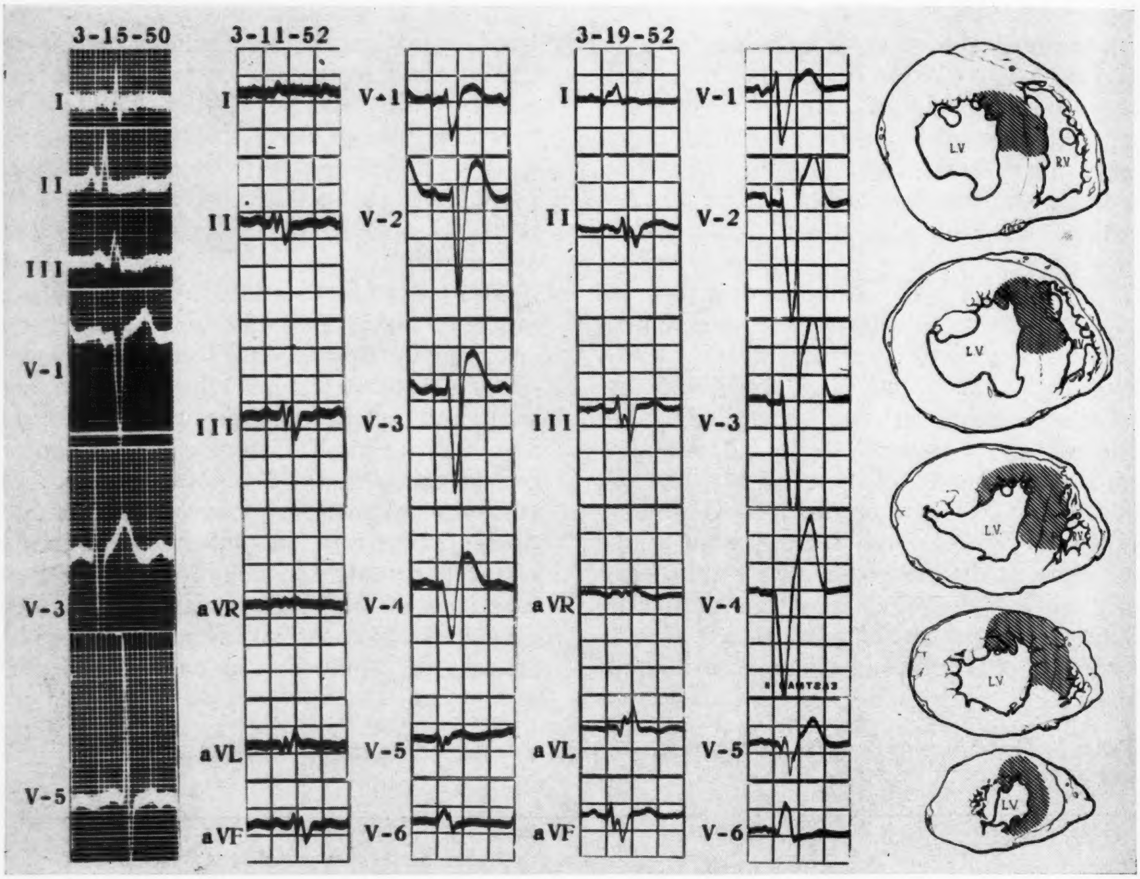

Fig. *1*. The patient, a 64-year-old man, died on March 24, 1952. He had experienced severe thoracic pain and a large anteroseptal infarction on March 8, 1952. The heart weight was 710 grams; expected weight, 265 grams. Note Q wave in Leads I, aV_L, and V_6 on March 19, 1952, with a small or absent R wave over the central precordium and the appearance of an R wave in Lead V_1 after left bundle-branch block and septal infarction.

this estimate was correlated with the clinical history in determining the probable date of the infarction. All clinical records were reviewed.

Augmented unipolar limb leads and Leads V_2, V_4, and V_6 were not available for one patient with a large recent anteroseptal infarct and for 5 patients with small infarcts.

Results

Table I summarizes the data obtained in this study. Significant facets of these data are here reviewed.

A Q wave was present in Lead I in 8 of the 39 cases. A large anteroseptal infarct was present in each of these same 8 cases, being recent in 3 (Fig. 1) and old in 5. In addition to a large old anteroseptal infarct, a large recent lateral infarct was present in 1 case (for electrocardiograms in this case, see Fig. 8, Case 30 in Reference 4), and a large recent posterior infarct was present in another case (Fig. 2). The septal portion of the infarct was large in 5 cases and small in 3. This evidence indicates that when a patient with myocardial infarction has left bundle-branch block associated with a Q wave in Lead I, the infarct will be confined to the anteroseptal region or have an anteroseptal component.

How consistently does anteroseptal infarction result in the production of a Q deflection in Lead I when left bundle-branch block also is present? In this series, 3 of 6 recent and 5 of 7 old large anteroseptal infarcts were associated with such a deflection. However, of the 24 patients having either a large or a small anteroseptal infarct, only 8 showed a Q wave in Lead I, and in all of these 8 patients the infarct was large.

A Q wave was present in Lead aV_L in 14 of the 33 cases in which this lead was recorded. A large infarct was present in 9 cases and a small one in the other 5. In 12 of the 14 cases the infarct was anteroseptal in position. Nine of the anteroseptal infarcts were old and 3 were recent. In addition to a large anteroseptal infarct, a large lateral infarct was present in one case and a large posterior infarct in another case. In the 2 cases in which there was a Q wave in Lead aV_L, but no anteroseptal infarct, the infarct was small and lateral in position in one case and small and posteroseptal in position in the other.

This evidence indicates that when a patient with myocardial infarction has left bundle-branch block and a Q wave in Lead aV_L, almost certainly the infarct involves the anteroseptal or lateral wall of the left ventricle; there was only one exception to this generalization in 14 cases.

How consistently does anteroseptal or lateral-wall infarction result in the production of a Q deflection in Lead aV_L when left bundle-branch block is also present? Twelve of 21 instances of anteroseptal infarction and 2 of 4 instances of lateral-wall infarction were associated with such a deflection, whereas in only 2 of 11 instances in which posterior, posteroseptal, or circumferential subendocardial infarction was present did a Q wave appear in Lead aV_L.

A Q wave was present in Lead V_6 in 5 of the 33 cases available for study. A large anteroseptal infarct was present in each of the 5 cases; it was recent in 2 and old in 3. In 1 case a large recent posterior infarct was present in addition to a large old anteroseptal infarct. A Q wave was also present in Lead V_5 in all 5 cases, whereas in none of the 5 was a Q wave present in Lead V_4.

This evidence indicates that when a patient with myocardial infarction and left bundle-branch block has a Q deflection in Lead V_6, the infarct will be confined to the anteroseptal region or have a large anteroseptal component.

How consistently is anteroseptal infarction associated with a Q deflection in Lead V_6 when left bundle-branch block is present? In this series, 5 of 12 patients with large anteroseptal infarction had such a deflection. However, of the 21 patients who had either a small or a large anteroseptal infarction, and in whom Lead V_6 was recorded, only 5 had a Q wave in this lead.

An rsR′ wave form in Lead V_6 was present in 2 of the 33 cases available for study; a large old anteroseptal infarct with a large septal component was present in both cases, and a large recent lateral

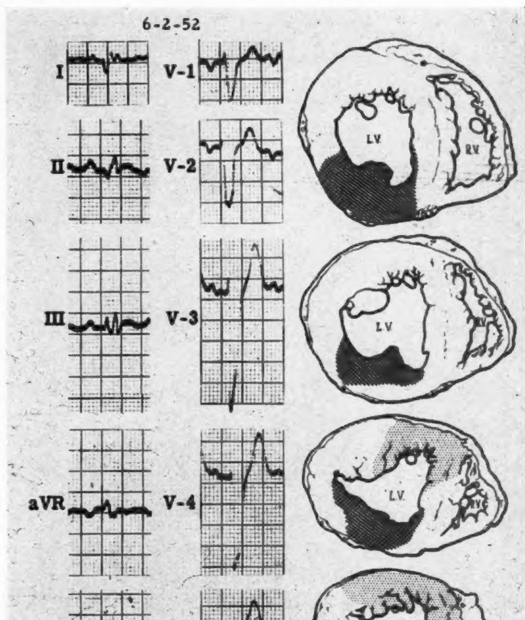

Fig. 2. The patient, a 66-year-old man, died on June 2, 1952. He was admitted to the hospital on the day of death because of ankle edema, which had been present for 1 day, and orthopnea, present for 3 weeks. Necropsy disclosed an old large anteroseptal apical infarct and a recent large transmural posterior infarct, about 2 days old as judged by histologic examination. There was a small subendocardial posterior infarct, 4 to 6 weeks old. The heart weight was 610 grams; expected weight, 345 grams. Note Q deflection in Leads I, aV_L, and V_6. The R wave in Leads V_4 and V_5 is very small, and late notching and slurring of the S wave in Lead V_4 are evident. Recent posterior infarction may be the cause of the elevated S-T segment in Leads III and aV_F. (Cross-sectional diagrams of the heart on the right-hand side of the figure are shown as viewed from above. Key to diagrams in this and subsequent figures: diagonal shading = acute infarction; stippling = old infarction.)

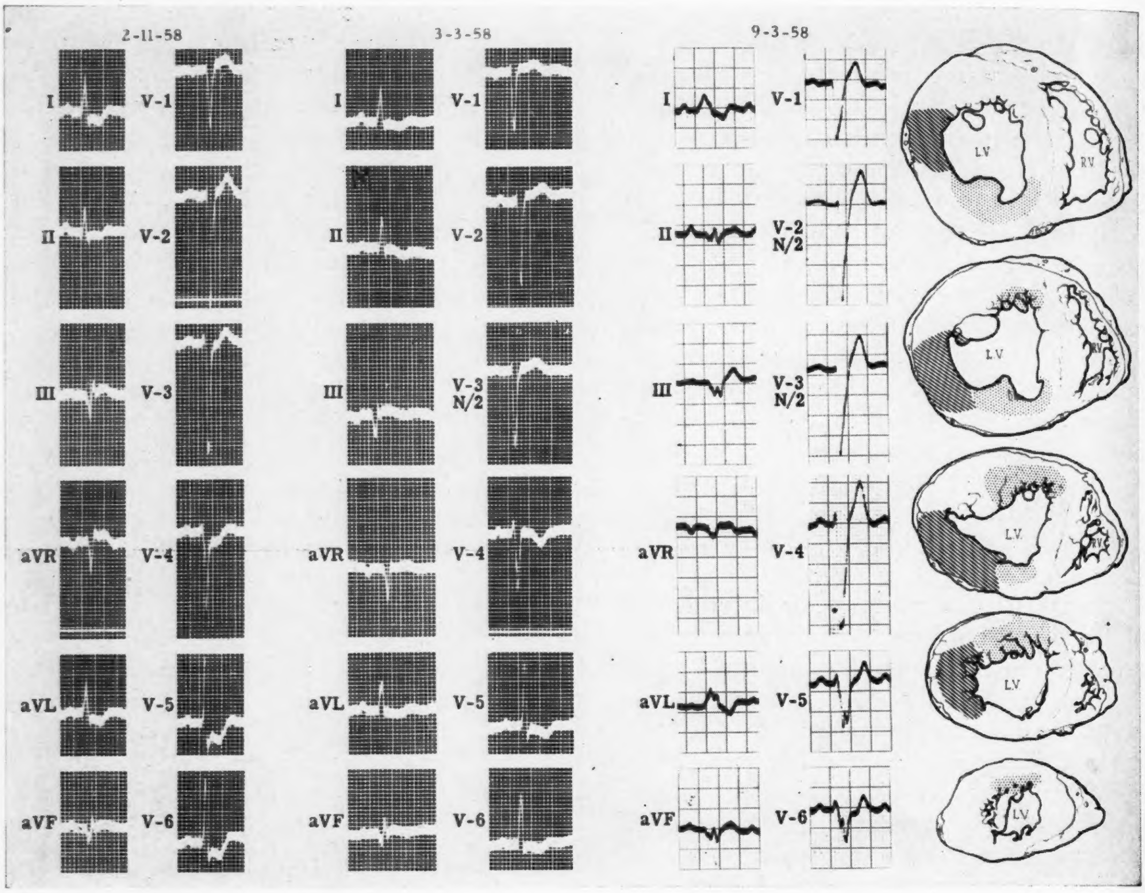

Fig. *3.* The patient, a 62-year-old man, died on Sept. 9, 1958. He had an old small anterior infarct and an old small subendocardial posterior infarct. A large transmural lateral infarction had occurred on Sept. 2, 1958. The heart weight was 465 grams; expected weight, 265 grams. The electrocardiograms of Feb. 11, 1958, reveal evidence of a posterior infarct of recent occurrence as well as R waves of low voltage in Lead V_1 through Lead V_4, probably related to the old anterior infarct. With the development of a lateral infarct and the onset of left bundle-branch block, the S-T segment is depressed in Lead I and in leads over the left precordium. The broad Q wave in Leads II, III, and aV_F on Sept. 3, 1958, may be a result of the old anterior and posterior infarcts plus the posterior component of the recent lateral infarction.

infarct was present in addition to the anteroseptal infarct in one of the 2 cases. An early downward notching of the upstroke of the R wave in Lead V_6, in the absence of a Q wave in this lead, was present in 2 of the 33 cases available for study; a large anteroseptal infarct with a large septal component was present in both cases, and, in addition, a large recent posteroseptal infarct was present in one of the 2 cases. Thus, the 5 of 12 cases of large anteroseptal infarction in which there was a Q wave in Lead V_6 becomes 9 of 12 cases when instances of Q waves and Q-wave equivalents are combined. Furthermore, none of 20 patients without transseptal infarcts had a Q wave or Q-wave equivalent in Lead V_6.

The R wave was lower in Lead V_3 or Lead V_4, or both, than in Lead V_1 or Lead V_2, or both, in 13 of the 39 cases. An anteroseptal infarct was present in 12 of the 13 cases; it was recent in 5 cases and old in 7, and it was large in 10 of the 12 cases. In the thirteenth case a small old lateral infarct and a very small recent anterior apical subendocardial infarct were present.

This evidence suggests that when a patient with myocardial infarction and left bundle-branch block has an R wave lower in Lead V_3 or Lead V_4, or both, than in Lead V_1 or Lead V_2, or both, the infarct almost certainly is anteroseptal in distribution. Furthermore, this finding appeared in 12 of 24 cases in which there was anteroseptal infarction, but in only

1 of 15 instances in which infarcts of other distributions were present.

A notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that showed an rS or QS form (usually Lead V_3 or Lead V_4) was present in 12 of the 33 cases available for study. An anteroseptal infarct was present in all 12 cases; it was recent in 3 cases and old in 9 cases, and was large in 10 of the 12 cases. A large posterior infarct was present in addition to a large anteroseptal infarct in 1 case, and the infarct was circumferential in another of the 12 cases.

A Q wave was present in both Lead II and Lead III in 3 of the 39 cases. A small posteroseptal infarct was present in one of these cases, a large lateral posterior infarct combined with small anterior and posterior infarcts in another (Fig. 3), and a small posterior infarct in the third.

Electrocardiograms which showed left bundle-branch block both before and after a recent infarction were available in 3 cases. In 2 cases (Figs. 4 and 5) the height of the QRS complex was markedly decreased. There was little change in the height of the QRS complex in any of the twelve leads in the third case, in which

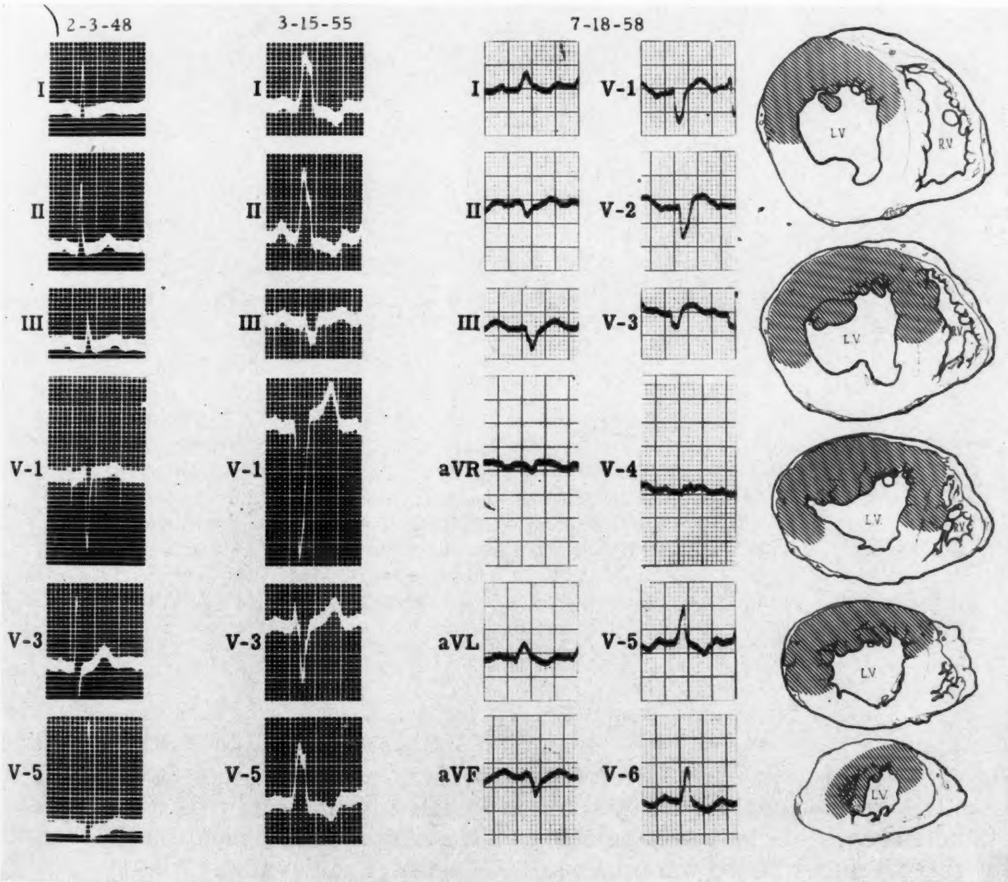

Fig. 4. The patient, an 88-year-old man, died on July 18, 1958. He had undergone laparotomy on July 7. He had experienced pulmonary edema and chest pain on July 18. Left bundle-branch block had been present on March 15, 1958. A large recent transmural anteroseptal infarct, about 10 days old as judged by histologic appearance, was found at necropsy. The heart weight was 570 grams; expected weight, 294 grams. There was marked decrease in the height of the QRS complexes on July 18, 1958, as compared with March 15, 1955. Note lack of an R-wave deflection in leads from the right precordium on July 18, together with a Q wave in Lead V_4. There is a small Q in Lead aV_L on July 18, but none in Leads I or V_6. The nearly isoelectric upright T in Leads I and V_6 after the infarction is in marked contrast to the segmental depression and T-wave inversion in these same leads recorded on March 15, 1955, before occurrence of the infarction. However, this change could be secondary to diminished area of QRS in these leads rather than to an ischemic effect

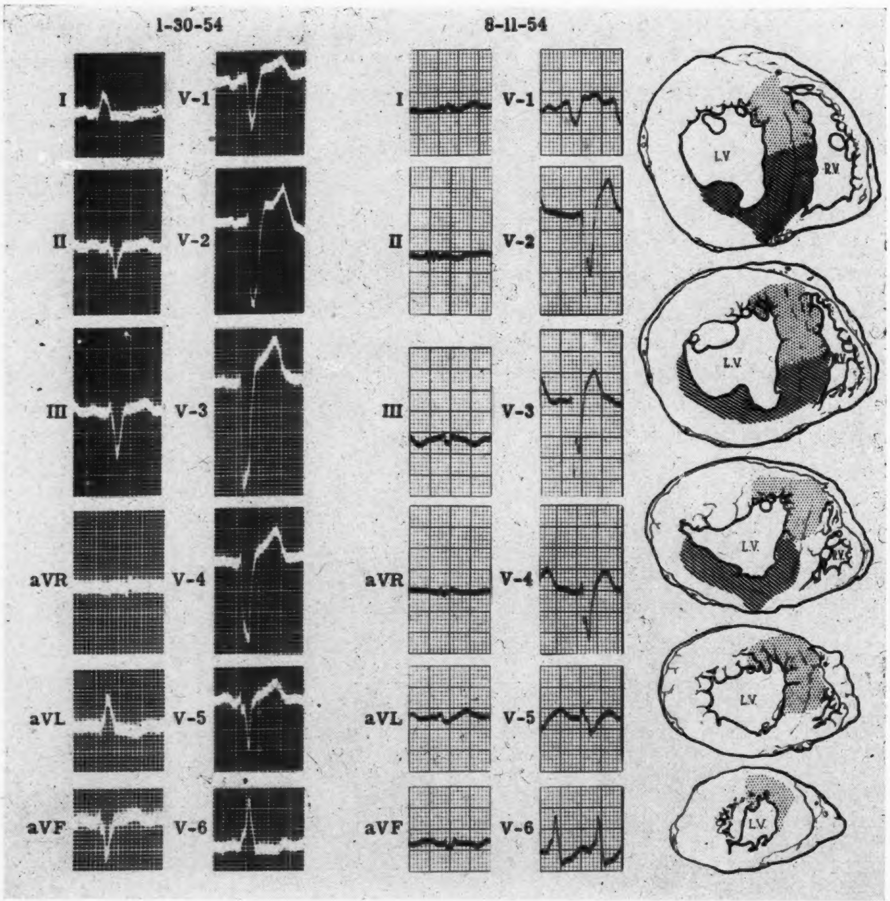

Fig. 5. The patient, a 59-year-old woman, died on Aug. 11, 1954. Angina pectoris had been present since April, 1953, and heart failure since January, 1954. Necropsy disclosed an old large anteroseptal transmural infarct. Left bundle-branch block was present before occurrence of a small transmural posteroseptal basal infarction on Aug. 10, 1954. The heart weight was 650 grams; expected weight, 306 grams. Note marked decrease in the height of the QRS complexes, especially in the standard and unipolar limb leads, on Aug. 11, 1954. The Q wave in Lead aV_L and Q-wave "equivalents" in Lead V_6 on both January 30 and August 11, and the Q-wave "equivalent" in Lead I on August 11, are probably related to the extensive septal infarct. Note late notch in Lead V_3 on August 11.

there was a small transmural posterior infarct.

Electrocardiograms taken before a recent infarction, but also before the development of left bundle-branch block, were available in 10 of the 39 cases. There was marked reduction in the height of the QRS complexes in Leads V_3 and V_5 in 1 case after a large anteroseptal infarction. There was little or no change in the height of the QRS complexes in the other 9 cases, even though the infarcts in 4 of the 9 were large and anteroseptal in position.

S-T-segment changes related to a recent anterior infarction were found in 4 cases. However, the S-T segment was elevated 1 mm. or more in Lead I in only 1 of the 39 cases. A small old posterior infarct and a large recent anteroseptal infarct were present in this case (Fig. 6). This was also the only case in which the S-T segment in Lead V_6 was elevated.

S-T-segment changes believed to be related to recent posterior infarction were found in 3 cases, tracings from 2 of which are reproduced in Figs. 2 and 3.

Comment

The results reported provide a basis for localization of a myocardial scar or infarct in a patient who has such a lesion. Because cases of left bundle-branch block without

myocardial infarction were excluded from the study, the diagnostic specificity of a certain electrocardiographic finding for infarction or scarring cannot be derived directly from our data. However, strong inferential evidence of infarction would appear to be afforded by certain of these data. The consistent appearance of certain electrocardiographic changes in the presence of a large infarct of uniform location, and the absence of these electrocardiographic changes when only a small infarct of similar location or a large infarct of different location was present, indicate, we believe, diagnostic reliability of the electrocardiographic finding. Instances of this kind were as follows:

1. A Q deflection in Lead I occurred in 8 of the 39 cases. In each of these cases a large transmural anteroseptal infarct was present. A Q wave did not occur in 26 cases (total of 39 minus 13 with large transmural anteroseptal infarcts) in which a large anteroseptal infarction was lacking.

2. A Q deflection or a Q-wave equivalent was present in Lead V_6 in 9 of 33 cases in

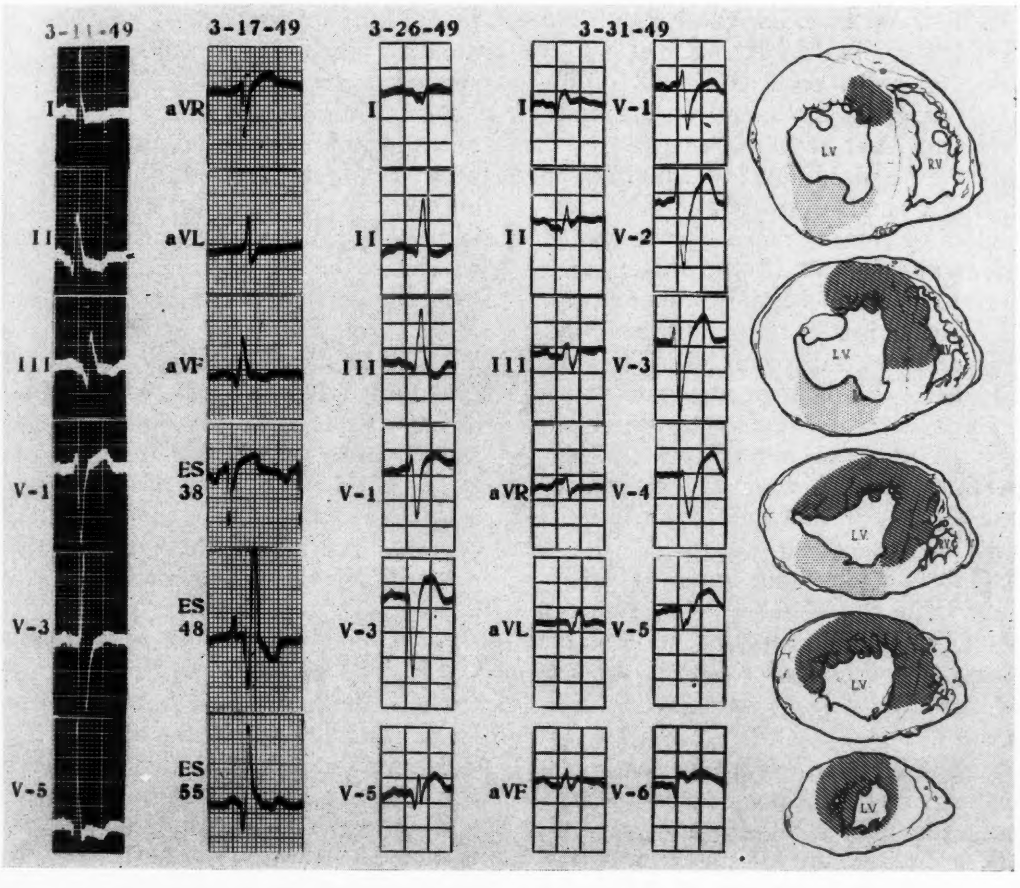

Fig. 6. The patient, a 65-year-old man, died on April 2, 1949. He had had angina pectoris since July, 1948. He became cyanotic on March 22, 1949, while undergoing abdominal operation. Necropsy revealed an old small transmural posterior infarct and a recent large transmural anteroseptal infarct, about 10 days old as judged by histologic appearance. The heart weight was 740 grams; expected weight, 415 grams. In the electrocardiograms of March 11 and March 17, note the Q wave in Leads II, III, and aV_F and in esophageal leads, with a prolonged QRS in these leads, indicating posterior infarction with postinfarction block. On March 26, 1949, after anteroseptal infarction, there is no R wave in Leads I and V_3 and the QRS complex is prolonged in these leads, probably indicating anterior postinfarction block. On March 31, 1949, the QRS interval has again increased and a major change has occurred in the mean QRS in the frontal plane. A Q wave is no longer present in Leads III and aV_F, but is present in Leads I, aV_L, and V_6. Note the almost absent R wave in Lead V_4 and the late notch and slurring in Lead V_5 on March 31, 1949, and the suggestion of elevation of the S-T segment in Leads I and V_6, the T wave being upright.

which this lead was recorded. In each of these 9 cases a large transmural anteroseptal infarct was present. Such deflections did not occur in 21 cases (total of 33 minus 12 with large transmural anteroseptal infarcts) in which a large anteroseptal infarct was lacking.

Of somewhat lesser reliability are the instances in which a certain electrocardiographic finding occurred predominantly in the presence of a large infarct of uniform location, but occurred also in instances in which a small, similarly located infarct was present. Into this category would fall instances of the following types:

1. An R wave in Lead V_3 or Lead V_4, or both, lower than an R in Lead V_1 or Lead V_2, or both, occurred in 13 of 39 cases. A large anteroseptal transmural infarct was present in 10 of these 13 cases, a small anteroseptal infarct in 2 additional cases, and a small old lateral infarct accompanied by a very small recent apical subendocardial infarct in the other case.

2. A notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that showed an rS or QS form was present in 12 of 33 cases available for study. In all of these 12 cases an anteroseptal infarct was present; in 9 the infarct was large and transmural, in 2 it was small, and in 1 it was large but subendocardial.

3. A Q wave was present in both Lead II and Lead III in 3 of 39 cases. A large lateral posterior infarct was present in one of these cases, a small posteroseptal infarct in one case, and a small posterior infarct in the third.

Of least reliability are those instances in which a given deflection occurred usually in association with a large infarct of uniform location but not infrequently in association with small infarcts of the same location and occasionally in association with infarcts of entirely different location. Into this category would fall instances in which there was a Q deflection in Lead aV_L. This deflection occurred in 14 of 33 cases: in 9 of which there were large transmural anteroseptal infarcts; in 3, small anteroseptal infarcts; in 1, a small lateral infarct; and in 1, a small posteroseptal infarct.

Summary of data for all three of the categories just reviewed discloses that 24 of the 39 cases included in this study presented one or more of the electrocardiographic findings held to afford evidence of greater or lesser reliability of myocardial infarction. Of the 18 cases in which infarcts were large, 15 presented one or more of these electrocardiographic findings, whereas 9 of 21 cases in which infarcts were small so qualified.

Summary

On the basis of a study of the pathologic, electrocardiographic, and clinical data in 39 cases in which there was a confluent myocardial infarct in the presence of left bundle-branch block, the following observations are made:

1. Substantial evidence of transmural anteroseptal myocardial infarction in the presence of left bundle-branch block would appear to be afforded (a) by a Q deflection in Lead I or (b) by a Q deflection or Q-wave equivalent in Precordial Lead V_6.

2. Supportive evidence of anteroseptal myocardial infarction in the presence of left bundle-branch block would appear to be afforded (a) by an R wave in Lead V_3 or Lead V_4, or both, that is, lower in amplitude than an R wave in Lead V_1 or Lead V_2, or both, or (b) by a notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that shows an rS or QS form.

3. Supportive evidence of infarction involving the posterior wall of the left ventricle in the presence of left bundle-branch block would appear to be afforded by a Q deflection in Standard Leads II and III.

4. Equivocal evidence of anteroseptal infarction in the presence of left bundle-branch block would appear to be afforded by a Q deflection in Lead aV_L.

5. In two of three instances in which electrocardiograms showing left bundle-branch block were recorded both before and after myocardial infarction, the height of the R waves in the standard leads decreased markedly.

6. Changes in S-T segments and T waves of a degree to be considered suggestive of myocardial infarction occurred in a minority of cases in which myocardial infarcts were recent.

7. The weight of every heart was more than the weight expected for the height, body weight, and sex of the patient. The mean increase in the weight of the heart over the expected weight was 100 per cent.

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High-frequency components in the electrocardiograms of normal subjects and of patients with coronary heart disease

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A wide-band recorder with an expanded time scale for recording the electrocardiogram reveals high-frequency components in the QRS that do not appear in the conventional electrocardiogram.[1-3] The greater incidence of such high-frequency components in patients with coronary heart disease when compared with a group of normal subjects used as controls was first reported in 1953[4] and subsequently confirmed.[5,6]

High-frequency components in the QRS recorded with adequate instrumentation consist of small, fast notches, slurs, and segments of high velocity. These phenomena, which are 1 to 7 milliseconds in duration, have been quantified by means of both high-pass and low-pass electronic filters.[6] It is the purpose of this paper to report on the number of high-frequency notches and slurs in the electrocardiograms of 104 patients with clinical evidence of coronary heart disease as compared with the incidence of these high-frequency components in 100 normal subjects who served as controls.

Materials and methods

One hundred four subjects with clinical evidence of coronary heart disease were studied. Eighty-eight had well-documented histories of myocardial infarction and typical electrocardiographic changes. The other 16 had the clinical symptoms of angina pectoris on exertion, with normal electrocardiograms when at rest, but definitely positive postexercise electrocardiograms. None of the patients had evidence of congenital, rheumatic, or syphilitic heart disease. The ages ranged from 43 to 75 years, with a mean of 56 years. There were 92 male and 12 female subjects. All of these were fully ambulatory. Approximately one half of the group were normotensive, and none was severely hypertensive, since we intentionally excluded the latter from this study. Sixty-four had normal heart size by x-ray examination, whereas 40 showed slight to moderate enlargement. Twenty-six patients were receiving digitalis. The electrical axis in the frontal plane ranged from +80 to −60 degrees. Subjects with bundle branch block were excluded from this study.

The control group consisted of 100 individuals who were free from cardiovascular disease as determined by past history, present signs or symptoms. There were 95 male and 5 female subjects. The age range was 40 to 65 years, with a mean of 52 years.

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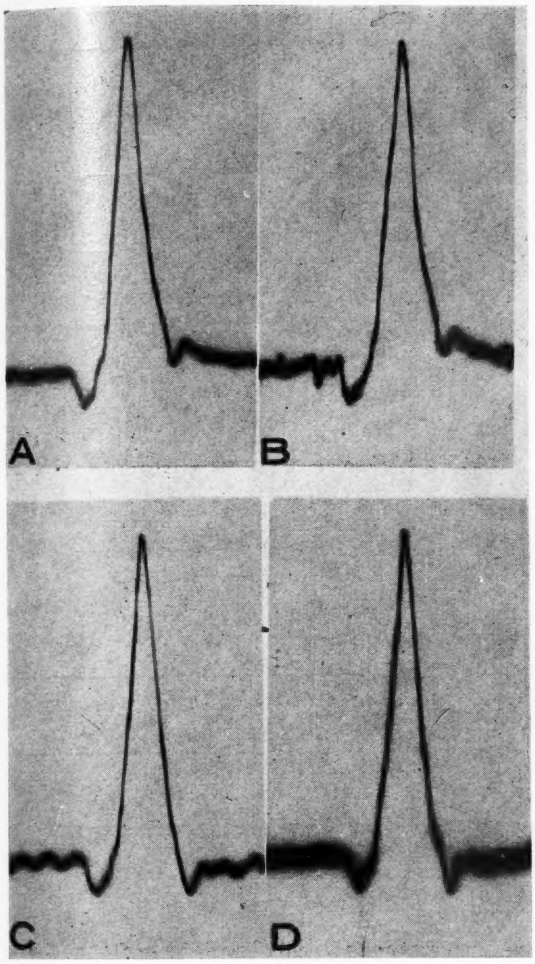

Fig. 1. *A*, Original signal, Lead II. *B*, The original signal plus muscle tremor induced by tensing the right forearm. *C*, The original signal plus 60-cycle interference seen in the base line. *D*, The original signal plus 120-cycle interference seen in the base line. In these records there is no significant notching or slurring of the R wave despite base-line noise.

The heart size was normal by x-ray examination, and the conventional electrocardiogram was negative. The electrical axis in the frontal plane ranged from +90 to −10 degrees. All members of this group are designated as normal in the tables of this paper and Appendix II.

Twelve scalar leads from the standard electrode positions were made with a wide-band recorder, having a frequency response flat to 1,000 cycles per second and down 6 decibels at 5,000 cycles per second as previously described.[1,2,4,6] This is in sharp contrast to most direct-writing electrocardiographs now in use which are relatively unresponsive at 100 cycles per second.* The amplification was regulated so that the QRS deflection traversed about 75 per cent of the cathode-ray screen. Thus, all the leads were made as large as possible. The relative size of any lead was determined by the height of its accompanying millivolt standardization signal.

An expanded time scale was obtained by using a paper speed of 350 mm. per second, which is 14 times the speed of the conventional electrocardiogram.[1] Records were made with Kodak Linagraph Paper No. 697, which is 5 inches wide. This was microfilmed and projected on a screen at

*See Appendix I for a discussion of the relation of frequency response to the distortion of notches of short duration.

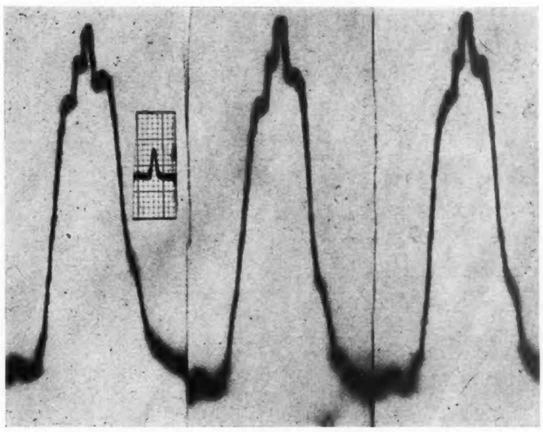

Fig. 2. Illustrates three marked notches near the peak of the R wave. There is also slight slurring at the peak and on the downstroke of the R wave. Three successive complexes are shown to demonstrate the repetitive nature of the high-frequency components. The small complex was made with a direct writer.

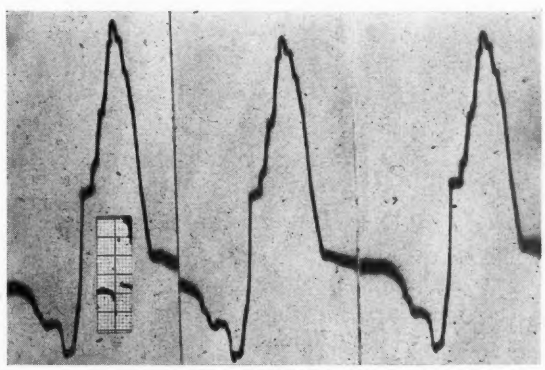

Fig. 3. Illustrates two notches in the Q wave, seven notches and/or slurs in the R waves. Three successive complexes are shown to demonstrate the repetitive nature of the high-frequency components. The small complex was made with a direct writer.

Table I. *High-frequency components in limb leads*

Number of components	Lead I				Lead II				Lead III				aV_R				aV_L				aV_F				Largest limb lead	
	N		A		N		A		N		A		N		A		N		A		N		A		N	A
	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L		
0	30	32	8	20	8	47	6	7	14	10	5	2	18	48	9	23	19	14	3	6	6	21	3	3	68	24
1	16	13	3	13	1	22	6	13	12	5	3	6	6	12	11	11	12	5	7	8	5	20	7	5	21	18
2	3	2	4	15	6	12	9	23	22	3	16	11	2	6	5	11	20	3	16	11	11	16	19	8	10	19
3	1		3	8	3	2	10	10	15	3	13	11	1		7	5	7		5	7	5	7	13	10	1	21
4			8	5			3	4	6		6	4	1		1	2	1		5	3			5	3		7
5							1	3	2		6	3				1			1	3			3	1		4
6							2	1											1				2			

N: Normal. A: Abnormal. S: Small Lead. L: Large Lead.

Table II. *High-frequency components in precordial leads*

Number of components	V_1		V_2		V_3		V_4		V_5		V_6	
	N	A	N	A	N	A	N	A	N	A	N	A
0	41	24	51	19	52	21	70	34	81	33	88	35
1	30	17	23	19	29	19	13	15	8	19	4	22
2	16	27	20	37	11	23	14	16	4	19	3	21
3	8	27	6	15	8	23	1	11		16		9
4	2	5		6		7		8		6		6
5	1	3		2		3		6		1		2
6				1		1		3				

N: Normal. A: Abnormal.

close range by means of a wide-angle lens so that the record for final viewing was 15 inches tall, or three times the size of the original photograph. This technique greatly facilitated reading because it eliminated the need for rolling and unrolling yards of unwieldy paper, and because it enlarged the original record. The time scale of the record when this optical system was used was very close to 1 millimeter per millisecond.*

In the rapidly moving portion of the QRS there are notches and slurs that are

*For those interested in trying this technique, 35-mm. transparent film is recommended in place of the 5-inch Linagraph Paper used by us. This film consumes less space and can be used to project the record to any desired size. However, in recording, a rapid film speed of 200 to 300 mm. per second must still be used to preserve the expanded time scale.

Table III. *Combined total of high-frequency components in V_5, V_6 and largest limb lead*

Number of components	Number of abnormal subjects	Number of normal subjects
0	11	66
1	8	16
2	10	11
3	10	5
4	13	2
5	8	
6	11	
7	4	
8	8	
9	5	
10	1	
11	3	
12	1	

equaled or even exceeded by the width of the base line. Therefore, it is necessary to take precautions that a true heart signal is present rather than an artifact due to noise. To identify true cardiac potentials, one can make use of their repetitive characteristic in successive QRS complexes. Only notches or slurs which are clearly repetitive in several successive cycles are read as true cardiac potentials. On the other hand, artifacts usually due to muscle tremor occur at random, and the notching in each successive QRS complex is in a different form and place. With experience, there is no problem in distinguishing between artifacts and true cardiac potentials of high frequency. However, if marked muscle tremor is present due to dyspnea, shivering, anxiety, thyrotoxicosis, neurologic disease, or senility, the record usually becomes unreadable for high-frequency components because they are masked by the noise. This is true for both direct visual inspection of the time voltage records and for spectral analysis.[6]

Fig. 1,*A* shows Lead II of a healthy 20-year-old woman without signs or symptoms of heart disease. There are no significant high-frequency components present in the QRS. Fig. 1,*B* shows the same lead as Fig. 1,*A*, plus self-induced muscle tremor. *C* and *D* of Fig. 1 show the same lead as *A*, plus increased base-line noise due to 60-cycle and 120-cycle interference, respectively, introduced from an oscillator. Artifacts of this amplitude in the base line produce no significant high-frequency alteration in the R wave. If the base line shows noise in excess of that shown in *B* to *D* of Fig. 1, the tracing is usually considered to be unreadable for high-frequency components unless they are distinctly larger than the noise and, of course, clearly repetitive.

Results

Table I shows the number of notches and slurs in each of the limb leads for the normal and abnormal groups. The number of subjects for each lead totals less than 104 for the abnormal group and less than 100 for the normal group. This is because there was sufficient muscle tremor in a few leads to render them unreadable for high-frequency components, and, in a few instances, a simple failure in photographic technique caused the lead to be indistinct. In either case such a lead was omitted from Table I.

In the limb leads there is a distinction made between the three larger leads and the three smaller leads because notching is more common in smaller limb leads in both normal and abnormal subjects, as has been reported previously.[4,6] Among the limb leads, the lead of largest amplitude, which has an axis collinear with the direction of the maximal frontal plane QRS vector, gave the best discrimination between the normal and the abnormal individuals, since only one normal subject had three slurs in this lead, whereas 32 abnormal subjects had three or more notches and/or slurs. Table II shows the number of notches and/or slurs in the precordial leads. Of the precordial leads, V_5 and V_6 gave the best discrimination, in that no normal individual had three or

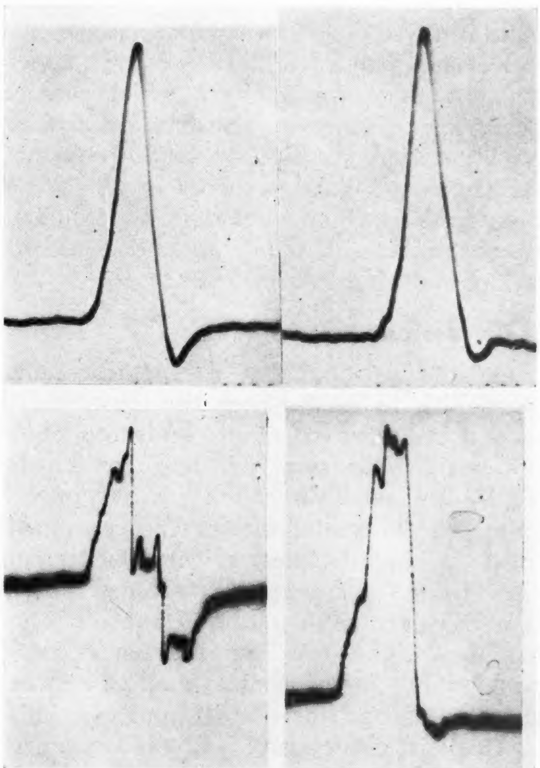

Fig. *4*. The upper R-S complexes are normal. They are V_5 and V_6 taken 2 years before infarction. The lower R-S complexes are V_5 and V_6 from the same individual 3 months after a well-documented episode of myocardial infarction. The appearance of high-frequency components, including very fast deflections in the lower two complexes, is self-evident.

more notches or slurs, whereas among the abnormal subjects there were 23 who had three or more such high-frequency components in V_5, and 17 who had them in V_6 (see Fig. 2). Leads V_2, V_3, and V_4 offered some discrimination when the number of notches considered to be abnormal was raised to four per lead (Fig. 3). The number of high-frequency notches and/or slurs per subject were counted for the combined total in Leads V_5, V_6, and the largest limb lead (see Table III). In the normal group, no individual had a combined total of five or more high-frequency components in these three leads. In the abnormal group, 41 had a combined total of five or more notches and/or slurs in these three leads, with a maximum of twelve and a mean of seven. In the 16 subjects with angina pectoris and normal resting conventional electrocardiograms, 7 had three notches in either the largest limb lead, V_5, or V_6. Each of the same 7 subjects had a combined total of five or more notches and/or slurs in these three critical leads.

Development of high-frequency notches or slurs may appear as a serial change occurring during myocardial infarction, as illustrated in Fig. 4. High-frequency serial changes have occurred in all of the 5 patients in whom we had an opportunity to obtain a wide-band, expanded record before and after infarction.

Discussion

On the basis of our results, it seems reasonable to establish as the upper limit of normal two distinct high-frequency notches and/or slurs per lead for Leads V_5, V_6, and the limb lead of greatest amplitude. The normal limit for the combined total of high-frequency components in these three leads is four per subject. There is a high probability that a subject who has more than two high-frequency components in one of these leads and more than four for all three leads, and who falls in the age groups studied, has coronary heart disease. The mathematical derivation of these probabilities is given in Appendix II.

The occurrence of serial change in the high-frequency electrocardiogram deserves serious consideration because it appeared to be due to coronary heart disease in the 5 cases observed by us. It is very possible that rheumatic myocarditis and other myocardial diseases which result in fibrotic changes can also produce both high-frequency components and serial changes, but we have not studied these diseases.

Judging from our subjects with angina pectoris, it is probable that for pre-employment, life insurance, or other types of examinations, where symptoms may be denied, about 40 per cent of the subjects with early coronary disease and negative conventional electrocardiograms will show high-frequency change when the method described in this paper is used. Therefore, this could serve as a diagnostic adjunct in detecting the probability of coronary heart disease. The normal group reported upon in this paper, with the addition of subjects each year, will serve, in time, to determine whether this method is of value for prognosis in people without known signs or symptoms of coronary heart disease.

Our figures do not relate to the gravity of prognosis or ultimate mortality, but to the probability that disease is or is not present. Even with 104 patients, we have had insufficient time and inadequate exposure to establish a valid ratio of mortality. However, certain statements do seem justified. The increase in incidence of high-frequency notching of the electrocardiogram in coronary disease seems more than can be explained by coincidence or chance fluctuation and, therefore, requires another explanation. In the absence of pathologic evidence of our own, we must draw on that of others in analogous situations. Durrer and associates[7] used a wide-band recorder and an expanded time scale, and studied experimental myocardial infarction with intramural and epicardial electrodes. They found abundant notching in the electrocardiogram. They stated that the excitation wave was desynchronized and fragmented, and that notching was due to dissimilar rates of conduction of the excitatory process. Burch, Horan, Ziskind, and Cronvich[8] have shown that there are changes in the vectorcardiogram not readily apparent in the conventional electrocardiogram in subjects with myocardial infarction. They found these changes due to smaller, less solid lesions. Zoll, Wessler, and Blumgart[9] have reported that, in

angina pectoris, patchy necrosis, or fibrosis, is a common lesion. We believe that comparable myocardial defects are most probably responsible for the abnormal number of high-frequency notches and slurs in the electrocardiograms of subjects with coronary heart disease.

Summary

Through the use of electronic and photographic equipment capable of recording a wide band of frequencies, from 0.01 to 5,000 cycles per second, it has been shown that subjects with clinical evidence of coronary heart disease have a much greater incidence of high-frequency notching and slurring in the electrocardiogram recorded with this high-fidelity equipment than do apparently normal subjects. The diagnostic possibilities of this method are discussed.

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Appendix I

David B. Geselowitz, Ph.D.

This paper deals with the occurrence of notches of between 1 and 7 milliseconds duration in the electrocardiogram of human beings. Such notches will not be observed in tracings recorded on most conventional electrocardiographs unless they are very large in amplitude, and even in this case they will be grossly attenuated and distorted. In order to determine the frequency requirements of a system including an amplifier and recorder which will satisfactorily pass notches of short duration, the following analysis was undertaken.

A simple low-pass filter is a network consisting of a single resistor and capacitor as shown in Fig. 5. This network has a frequency response

$$\frac{V_0}{V_i} = \frac{1}{\sqrt{1 + (2\pi fRC)^2}} = \frac{1}{\sqrt{1 + 3(f/f_c)^2}}$$

which falls to a value of one half at the 6-decibel frequency, f_c, where

$$f_c = \frac{0.275}{RC}$$

and falls off at a rate of 6 decibels per octave for frequencies much greater than f_c.

As a representative notch, consider a triangular pulse of unit amplitude and duration T as shown in Fig. 6. This pulse is described mathematically as

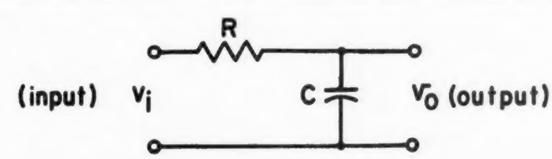

Fig. 5. Simple low-pass filter consisting of a resistor (R) and a capacitor (C).

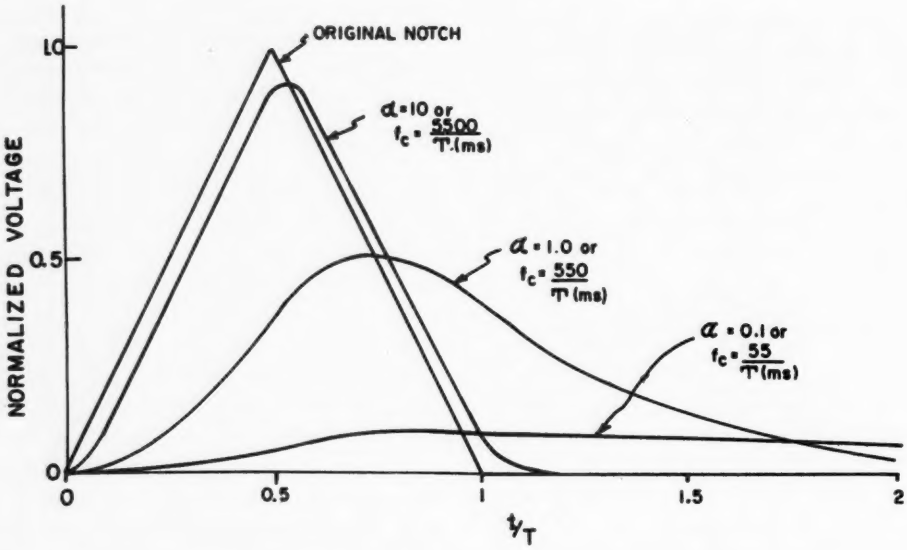

Fig. *6.* Response of low-pass filter with different 6-decibel cutoff frequencies, f_c measured in cycles per second, to triangular notch of duration *T*. Duration *T* and time *t* are measured in milliseconds.

$$V_i = \begin{cases} 2\frac{t}{T} & \text{for } \frac{T}{2} > t > 0 \\ 2-2\frac{t}{T} & \text{for } T > t > \frac{T}{2} \\ 0 & \text{for } t > T \text{ or } t < 0 \end{cases}$$

The change in this pulse after it passes through the filter can be calculated on the basis of techniques of transient circuit analysis. The resulting output, V_0, is found to be

$$V_0 = \begin{cases} 2\frac{t}{T} - \frac{2}{\alpha}(1-e^{-\alpha t/T}) & \text{for } \frac{T}{2} > t > 0 \\ 2-2\frac{t}{T} + \frac{2}{\alpha}\left[1 + (1-2e^{\alpha/2})e^{-\alpha t/T}\right] & \text{for } T > t > \frac{T}{2} \\ \frac{2}{\alpha}(1-2e^{\alpha/2} + e^{\alpha})e^{-\alpha t/T} & \text{for } t > T \end{cases}$$

where

$$\alpha = \frac{T}{RC} = \frac{f_c T}{0.275}$$

The result clearly depends on the parameter α, which, in turn, is related to f_c. Plots of V_0 for $\alpha = 0.1$, 1, and 10 are shown in Fig. 6. For a fixed pulse duration the output falls as the width of the band is decreased.

This effect is even more dramatic if the notch is superimposed on the ascending or descending portions of the R wave. Fig. 7 illustrates this point. Here a notch of 2.5-milliseconds duration is shown superimposed on an R wave which falls from its peak value to 0 linearly in 30 milliseconds. The notch is taken to have an amplitude of 10 per cent of that of the R wave. In part *a* the original signal is shown. The notch itself is shown at the base line. It is interesting to observe that the notch, when superimposed on the R wave, undergoes an apparent reduction in amplitude. This effect is enhanced as the pulse duration increases, and affords an explanation for the results described in connection

with Fig. 1,*B* in the text where moderate tremor in the base line was not apparent in the QRS.

The results of parts *b* and *c* are taken from data in Fig. 6. For f_c = 1,100 c.p.s. the notch is reproduced quite well (*b*), whereas for f_c = 110 c.p.s. it is reduced

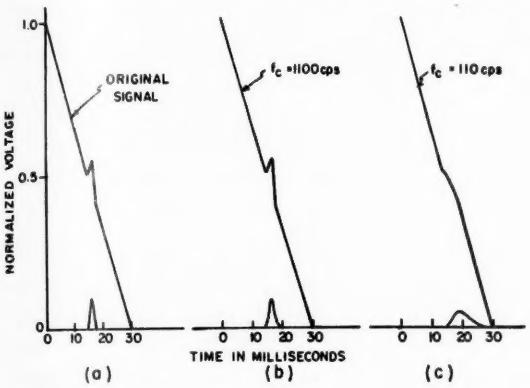

Fig. 7. Response of low-pass filter to triangular notch of duration 2.5 milliseconds superimposed on descending R wave for various values of filter cut-off frequency, f_c. (*a*) Original signal, or f_c infinite; (*b*) f_c = 1,100 c.p.s.; (*c*) f_c = 110 c.p.s. Small pulse on base line represents the notch itself.

more or less to a slur (*c*). For f_c = 11 c.p.s. there would be no discernible effect of the notch on the R wave; as a matter of fact, the R wave itself would be distorted.

Whereas most systems have frequency responses which fall off more rapidly than 6 decibels per octave, the present results are representative of those that would be obtained in general for a low-pass filter. As a rule of thumb, then, we conclude that to pass a notch without appreciable distortion, a low-pass filter must have a 6-decibel frequency f_c, measured in cycles per second of

$$f_c > \frac{2.5}{T} = \frac{2,500}{T(ms)}$$

while for

$$f_c < \frac{0.1}{T} = \frac{100}{T(ms)}$$

the notch may be missed entirely. For intermediate values, the pulse will be attenuated and distorted accordingly.

Appendix II. Statistical analysis of significance of high-frequency notching

*J. Alan Lauer, A.S.A.**

Leads V_5, V_6, and the largest limb lead were studied in greater detail because it appeared that the differences in the data for the normal and abnormal groups were greatest for these leads. Simple mathematical curves were fitted to the data for these leads reported in Tables I, II, and III. These curves serve to smooth out the random fluctuations in the reported data and also provide a means to extrapolate the data for normal subjects in order to estimate the probabilities of normal people having a high number of notches. Two characteristics of the data created some difficulty in fitting these curves. These were the small number of groups for the normal subjects (a maximum of 4 groups because only 0, 1, 2, or 3 notches were observed on any one of these leads), and the tendency to show about the same number of people with 1 notch as with 2.

Exponential curves of the type $Y = AB^x$ were fitted to the distributions for the normal subjects of notches on each of the three leads, and also to the distribution for the normal subjects of the sum of the notches on the three leads. Third-degree curves ($Y = ax^3 + bx^2 + cx + d$) were fitted to the distributions for the abnormal subjects of notches on Lead V_5 and the largest limb lead, and second-degree curves ($Y = ax^2 + bx + c$) were fitted to the distributions for the abnormal subjects of notches on Lead V_6 and the sum of the notches on the three leads. The curves in all cases were fitted by the method of moments.

The chi-square (χ^2) test was applied to these fitted curves in order to test the

*From the Actuarial Division, Provident Mutual Life Insurance Company of Philadelphia, Philadelphia, Pa.

Table IV. Probability of having a given number of notches on Lead V_5, Lead V_6, or the largest limb lead

Number of notches	Lead V_5		Lead V_6		Largest limb lead	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
0	.8454	.3561	.9048	.3628	.6944	.2508
1	.1307	.2061	.0861	.2636	.2122	.2220
2	.0202	.1904	.0082	.1799	.0648	.2019
3	.0031	.1839	.0008	.1119	.0198	.1739
4 or more	.0006	.0635	.0001	.0818	.0088	.1514

Table IVA. Probability of having a given total number of notches on Lead V_5, Lead V_6, and the largest limb lead

Number of notches	Normal	Abnormal
0	.6211	.1078
1	.2353	.1101
2	.0892	.1104
3	.0338	.1086
4	.0128	.1047
5	.0049	.0989
6	.0018	.0911
7 or more	.0011	.2684

Table V. Probability that a person with a given number of notches on Lead V_5, Lead V_6, or the largest limb lead falls in the abnormal class*

Number of notches	Lead V_5	Lead V_6	Largest limb lead
0	.04	.04	.04
1	.15	.25	.10
2	.51	.71	.26
3	.87	.94	.49
4 or more	.93	.99	.65

*From a statistical point of view, these probabilities apply only in the hypothetical situation in which no information is known except the number of notches on the specified lead or, in the case of Table VA, the sum of the notches on the three leads.

reasonableness of the fit. The test indicated an acceptable fit for Lead V_5 of the normal subjects, largest limb lead of the abnormal subjects, and the combination of the three leads for the normal subjects, and an excellent fit in the remainder of the cases, except Lead V_6 of the normal group. In this last instance it was not possible to apply the test since there were only three groups (0, 1, or 2 notches), and two of them were very small. However, the fitted curve appears to be a reasonable one for estimating the probability of a normal person having more than 2 notches on this lead.

Probabilities that a member of the normal or abnormal group would show a given number of notches on a given lead or the combination of three leads were determined from the fitted curves. These probabilities are shown in Tables IV and IVA.

In order to determine the probability that a person with a given number of notches does or does not have coronary heart disease, it was necessary to estimate

Table VA. Probability that a person with a given total number of notches on Lead V_5, Lead V_6, and the largest limb lead falls in the abnormal class*

Number of notches	Probability
0	.02
1	.05
2	.12
3	.26
4	.48
5	.69
6	.85
7 or more	.96

*From a statistical point of view, these probabilities apply only in the hypothetical situation in which no information is known except the number of notches on the specified lead or, in the case of Table VA, the sum of the notches on the three leads.

Table VI. Expected distribution of 1,000 people according to the number of notches on each of Lead V_5, Lead V_6, and the largest limb lead*

Number of notches	Lead V_5		Lead V_6		Largest limb lead	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
0	760.9	35.6	814.3	36.3	625.0	25.1
1	117.6	20.6	77.5	26.3	191.0	22.2
2	18.2	19.0	7.4	18.0	58.3	20.2
3	2.8	18.4	.7	11.2	17.8	17.4
4 or more	.5	6.4	.1	8.2	7.9	15.1
Total	900.0	100.0	900.0	100.0	900.0	100.0

*Based on same assumptions as Tables V and VA.

the proportion of the population from which these samples were drawn which would fall in the abnormal class. A study of the health records of the employees in the Home Office of the Provident Mutual Life Insurance Company indicates that 10 per cent would be a reasonable estimate of this proportion. On the basis of this proportion and the probabilities in Tables IV and IVA, the probabilities in Tables V and VA were calculated. These tables support the conclusion in the paper that any member of the population represented by this study who shows more than 2 distinct high-frequency notches and/or slurs on any one of the three leads in question, or a total of more than 4 such high-frequency components on these three leads, is very likely to have coronary heart disease.

Tables VI and VIA were derived as a byproduct of Tables V and VA and are shown here as a matter of possible interest. They show for a random sample of 1,000 people the expected number of people in the normal and abnormal classes with a given number of notches, based on the same assumptions as Tables V and VA.

Table VIA. Expected distribution of 1,000 people according to total number of notches on Lead V_5, Lead V_6, and the largest limb lead*

Number of notches	Normal	Abnormal
0	559.0	10.8
1	211.8	11.0
2	80.3	11.0
3	30.4	10.9
4	11.5	10.5
5	4.4	9.9
6	1.6	9.1
7 or more	1.0	26.8
Total	900.0	100.0

*Based on same assumptions as Tables V and VA.

Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology

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Detroit, Mich.

The electrophysiology of the atrioventricular node and bundle of His has been the subject of numerous recent interesting investigations.[1-32] As a result of these studies, two unsettled questions have emerged: (1) whether there is a system of dual transmission in this region, and (2) the nature of the slight delay in conduction observed in or near the A-V (atrioventricular) node. Morphologic research in this field has not kept pace with the elegant physiologic studies. This is a report of morphologic observations on the A-V node and its environs, in which particular attention was focused on those details which could contribute to a better understanding of its electrophysiology.

Material and Method

Eighty-one hearts from human subjects were studied. Three of the 81 were from infants, whereas the remainder were from adults who were between 18 and 82 years of age. Both normal and abnormal hearts were included. One or more electrocardiograms had been recorded in 76 of the subjects shortly before death.

For examination of the A-V node a bloc of tissue which extended from the noncoronary sinus of the aorta to the epicardium of the crux of the heart was removed; this bloc included at least 2 cm. of the interatrial and the interventricular septa. From this bloc of tissue, slices 2 mm. thick were cut perpendicular to the atrioventricular valve rings, which is also perpendicular to the junction of the interatrial and interventricular septa. From the aortic end of the bloc the first 6 to 10 slices usually included the undivided A-V bundle and the A-V node. Both of these structures may sometimes be seen with the naked eye, since they are located beneath the right atrial endocardium just posterior to the membranous portion of the interventricular septum.[33,34]

As with the sinus node, which was also studied in each case,[35] a variety of stains was employed but the most useful proved to be the Goldner modification of the Masson trichrome.[36] Photomicrographs were obtained with a Zeiss photomicroscope.

Results

For a representative concept of its shape, the A-V node of the human being may be thought of as a flattened oblong structure, concave on one side and convex on the other, somewhat like a tiny spleen (Figs. 1 and 2). The concave surface lies directly

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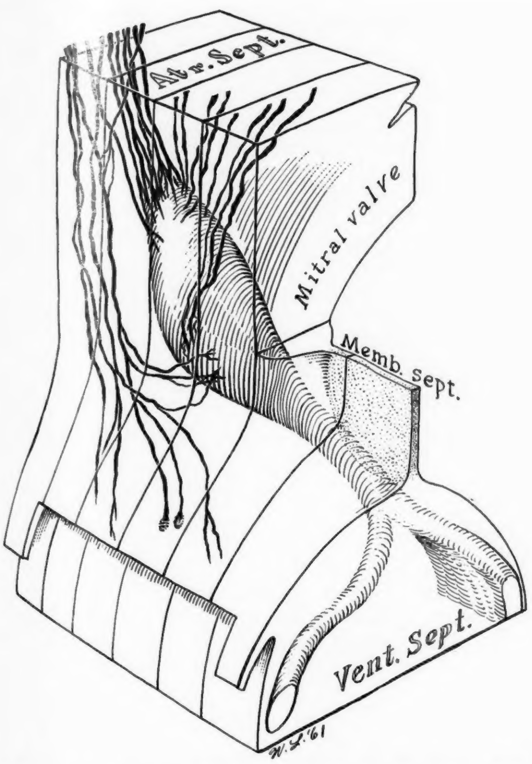

Fig. 1. A schematic drawing of the human A-V node, illustrating its relationship to the two atrioventricular valves and the interatrial and interventricular (including its membranous portion) septa. The A-V bundle divides into a single right bundle branch and multiple left bundle branches, as usual. Fibers from the central interatrial septal tracts and from the Eustachian ridge enter the posterior superior margin of the node, and also form bypass tracts, as described in the text. Note that some of the bypass tract fibers re-enter the inferior margin of the node, and that some terminate at the base of the tricuspid valve; rarely, some penetrate directly into the crest of the interventricular septum.

on the right atrial side of the central fibrous body, which is the anchor of the mitral annulus. The average dimensions of the A-V node in an adult human being are approximately 1 by 3 by 6 mm., but there is considerable variation in its size.

The posterior and superior margins of the node receive fibers from adjacent atrial myocardium. From the anterior and inferior margins of the node a bundle of parallel fibers (the bundle of His) come together and veer into the middle of the central fibrous body, at the same time descending toward the interventricular septum. In the central fibrous body the bundle of His measures about 1 mm. on cross section. When the bundle of His reaches the crest of the interventricular septum it becomes roughly triangular in cross section. It continues anteriorly to divide into the right and left bundle branches. The precise course of these branches has been well defined in several animals (notably the cow and sheep) but is more difficult to trace in man.

Within the center of the A-V node there is usually a major artery, but this is less constant in either its presence or its central location than is the sinus-node artery.[35] The substance of the node is almost entirely a profusely ramifying and interlacing group of striated fibers, which are shorter and broader than sinus-node fibers (Fig. 3). There is little collagen matrix in the A-V node, in contrast to the heavy concentration of collagen in the normal sinus node. At the anterior inferior end of the node the interlacing fibers become oriented parallel to each other to form the A-V bundle.

Two groups of fibers from the interatrial septum enter the A-V node from above and behind. The first group courses down the center of the interatrial septum and divides into two tracts just above the node. The larger tract passes directly into the node; the smaller tract deviates toward the right atrial endocardium. The second group of fibers comes primarily from the Eustachian ridge and also divides into two small tracts; one tract continues down the right atrial endocardium, bypassing the A-V node, whereas the other tract turns centrally to join the central septal fibers entering the posterior superior portion of the node. There is a decussation of tracts as the fibers from the Eustachian ridge turn centrally to cross those from the septum which turn toward the right atrial endocardium (Fig. 4). The septal tracts which turn to the right atrial endocardium join with the tracts from the Eustachian ridge which bypass the A-V node (Figs. 5 to 11).

There are numerous Purkinje fibers (Fig. 12) in all these tracts but also ordinary-appearing myocardial fibers which do not possess these characteristics. In the tracts descending from the Eustachian ridge down the right atrial endocardium around the A-V node there are numerous Purkinje fibers. These "bypass" tracts divide as they descend to the base of the tricuspid valve, which is virtually always

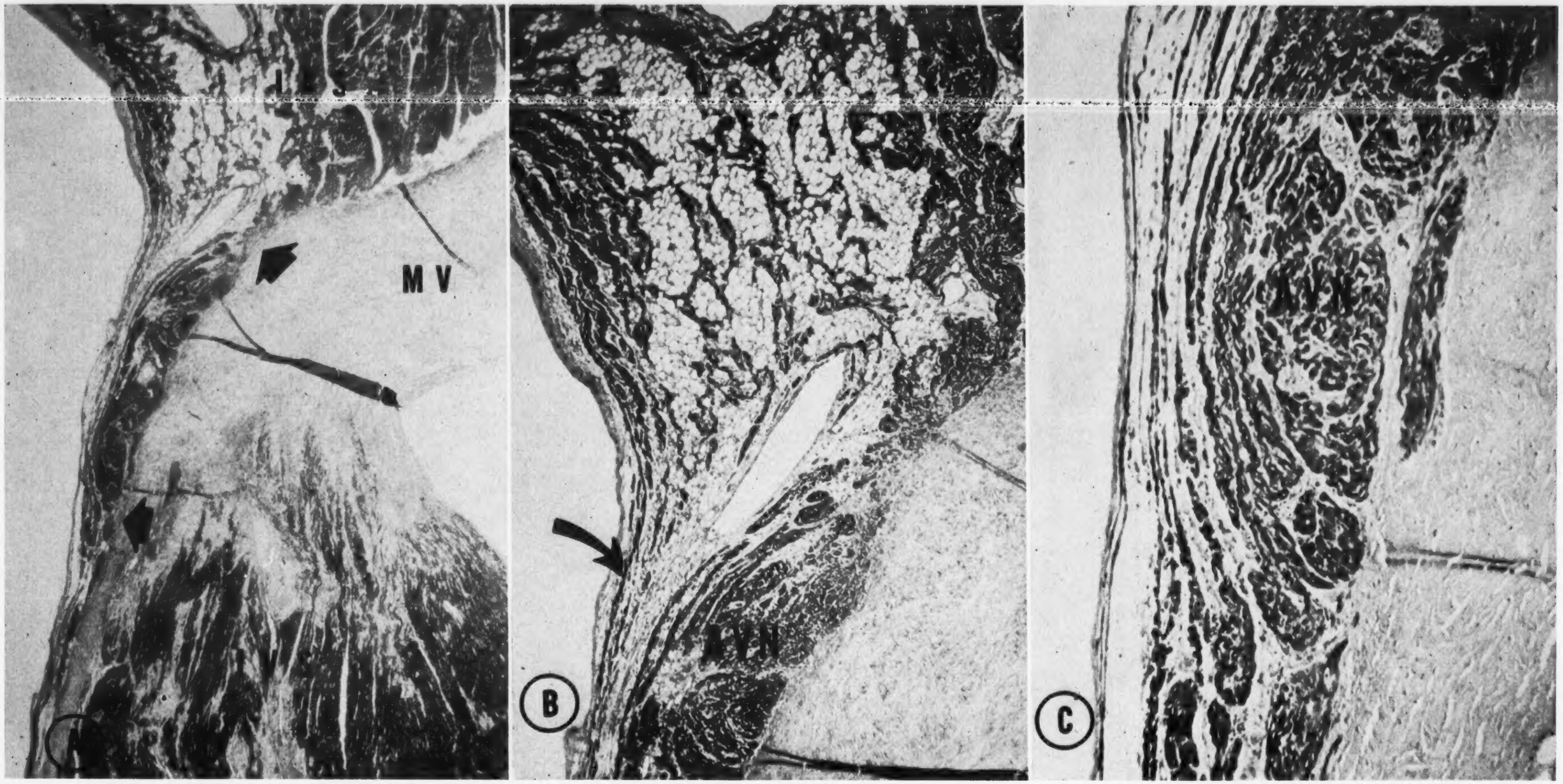

Fig. 2. Three views of the A-V node and its environs, from the heart of an 18-year-old boy. In *A* the central fibrous body, which is the anchor of the mitral valve (*MV*), lies between the interatrial septum (*IAS*) and interventricular septum (*IVS*). Opposite the mitral valve is the right atrial endocardium, along the left margin of the photograph. Just beneath the right atrial endocardium, lying directly on the central fibrous body, is the A-V node; tracts from the interatrial septum can be seen entering the node at the upper arrow, whereas the bypass tracts may be seen joining the inferior margin of the node at the lower arrow. The bypass tracts lie between the node and the right atrial endocardium, and fibers from them may be seen continuing to the bottom of the photomicrograph, enroute to the base of the tricuspid valve, which is out of the range of the photograph. *B* is a view of the upper portion of the node shown in *A*. Tracts from the Eustachian ridge occupy the upper left portion of the photomicrograph, descending along the right atrial endocardium to bypass the A-V node as indicated by the arrow. Tracts from the interatrial septum occupy the upper right portion of the photomicrograph and descend into the A-V node. Between the two tracts there is a lacy area of interweaving fibers (see text for discussion). In this and all subsequent photomicrographs, *AVN* indicates A-V node. *C* is a view of the lower portion of the node shown in *A*. The bypass tracts between the A-V node and the endocardium of the right atrium are shown re-entering the inferior margin of the node, which occupies most of the central portion of this photomicrograph, from top to bottom. (All stained with Goldner trichrome stain. *A*, ×4; *B*, ×10; and *C*, ×25.)

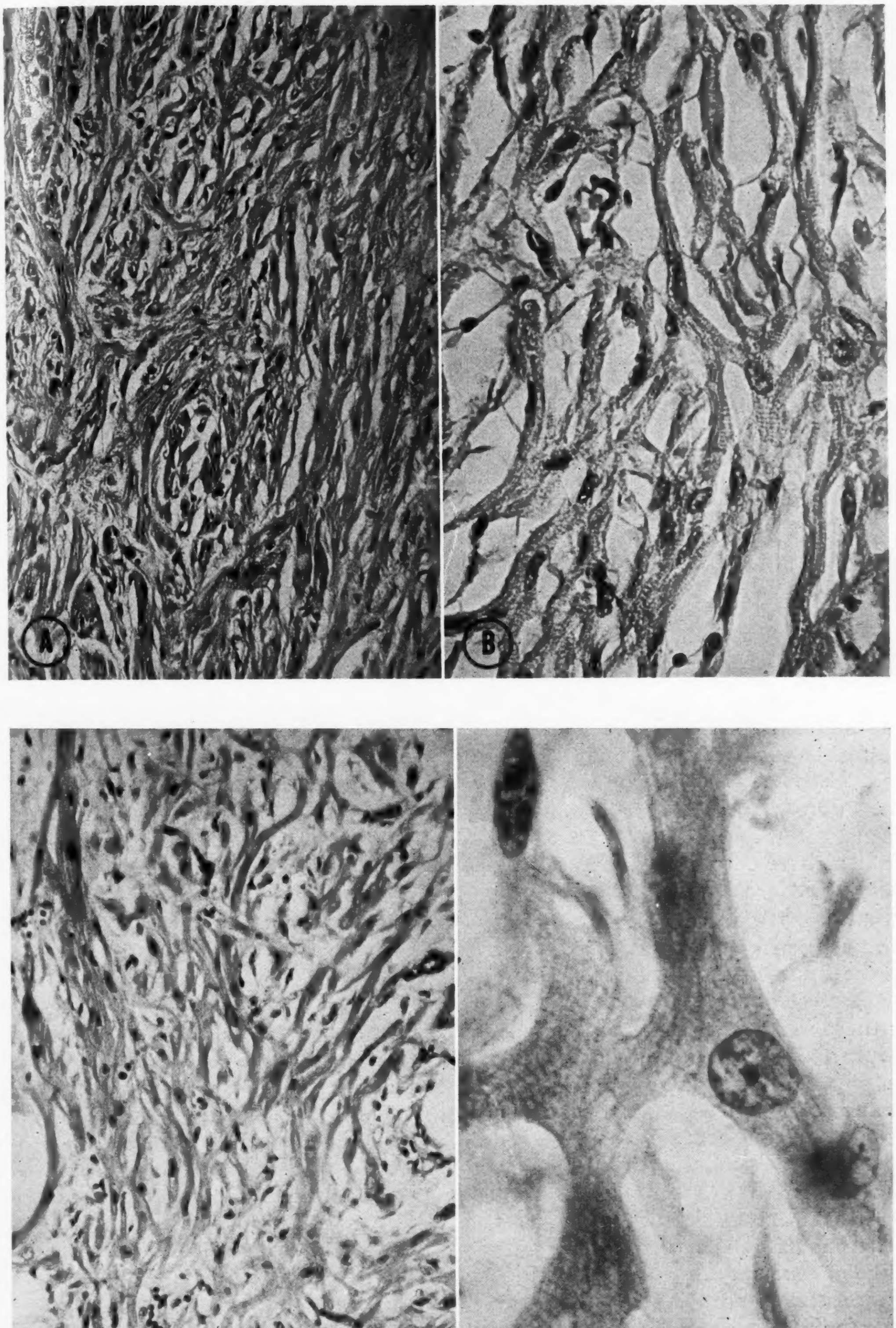

Fig. 3. Four views demonstrating the central architecture of the normal human A-V node. *A*, From a 60-year-old man. *B*, From a 56-year-old woman. *C* and *D*, From a 57-year-old man. Note the interconnections and arborizations. (All stained with Goldner trichrome. *A*, ×64; *B*, ×160; *C*, ×64; and *D*, ×400 [oil].)

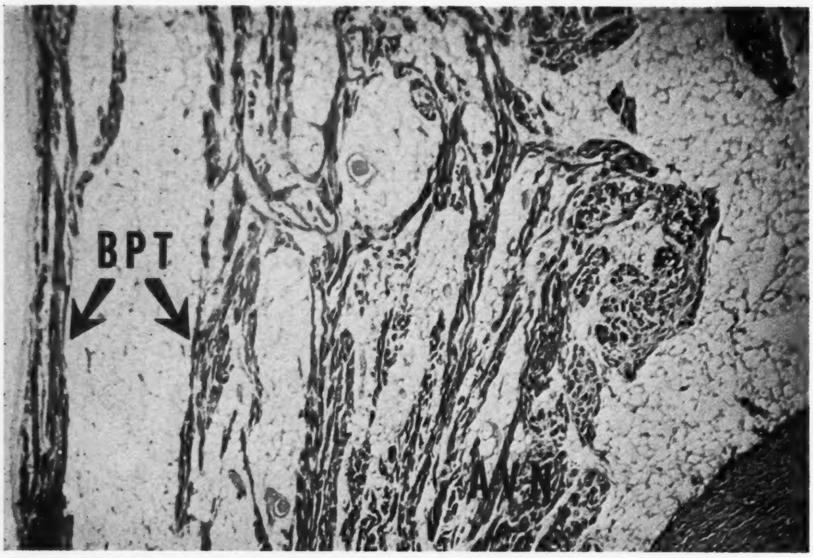

Fig. *4.* A view of the region between the lower interatrial septum and upper A-V node from the heart of a 49-year-old man. Decussation of the interatrial septal tracts which turn toward the endocardium, and of the tracts from the Eustachian ridge which turn toward the upper margin of the A-V node are well shown. The bypass tracts (*BPT*, here and in subsequent photomicrographs) pass vertically down the left margin of the photomicrograph, between the A-V node and right atrial endocardium.

below the level of the A-V node and considerably below the attachment of the mitral valve (on the opposite side of the central fibrous body). The two major divisions of the bypass tracts are into one group which re-enters the inferior margin of the A-V node, and a second group which terminates, often in a whorl, at the base of the tricuspid valve. Rarely, a few fibers from the bypass tracts penetrate directly into the crest of the interventricular septum; these were present in one heart from an adult and one heart from an infant in this study (Fig. 13). The only other direct communication of atrial with ventricular fibers, not passing through the A-V node, was encountered posterior to the A-V node in the hearts of two adults; these passed from central interatrial septal tracts directly through to the crest of the interventricular septum.

The posterior margin of the A-V node is never far from the opening of the coronary sinus, and sometimes directly abuts it. The anterior margin of the A-V node is almost inseparable from the A-V bundle, the most convenient distinguishing feature being the point at which the fibers cease interlacing and become parallel, a point at which the structure also veers centrally into the central fibrous body. The bundle continues for about 10 mm. in its descent to the crest of the interventricular septum before it begins dividing. This descent of the A-V bundle occurs along the posterior inferior margin of the membranous interventricular septum (Fig. 1).

Discussion

The microscopic anatomy of the normal human A-V node may help explain certain aspects of the electrophysiology of A-V conduction. Two pertinent anatomic features are the bypass tracts in the right atrial endocardium, and the profuse arborization of the fibers composing the node itself. This latter feature is well known.[37]

In Kistin's[38] study of the morphology of the A-V node, he noted the region here referred to as bypass tracts but stated that this was ordinary atrial myocardium. In at least half of the present cases, however, this region was predominantly composed of well-defined Purkinje fibers. Since sections were made only at 2-mm. intervals, the possibility that *all* of the hearts contain Purkinje fibers in these bypass tracts cannot be excluded.

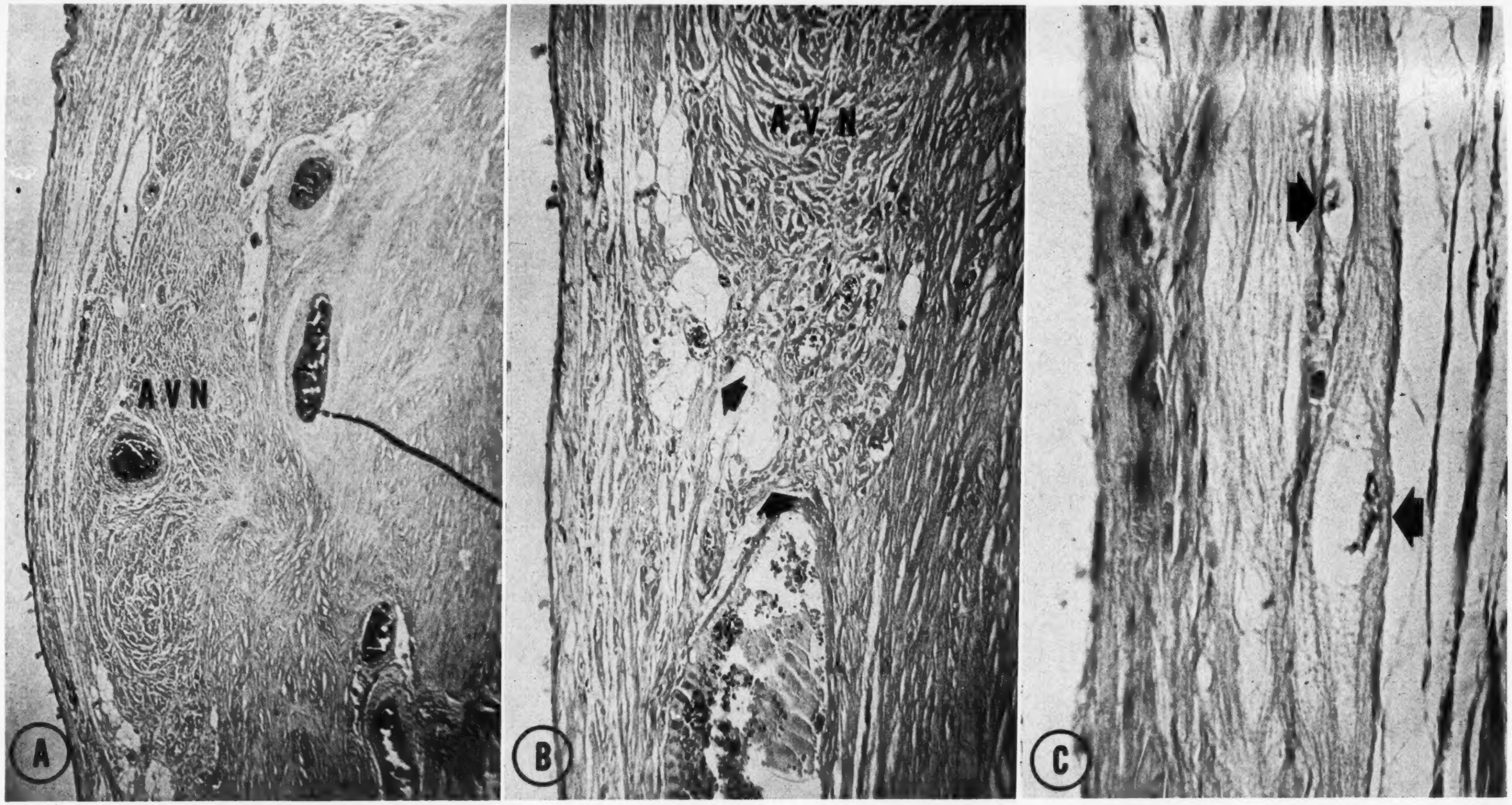

Fig. 5. Three views of the A-V node and its bypass tracts from the heart of a 38-year-old man. *A* is an orienting view, showing the A-V node between the central fibrous body and the right atrial endocardium. *B* is a view of the lower portion of the same node, with arrows indicating the connections between the node and the bypass tracts, which can be clearly seen passing along the right atrial endocardium. *C* shows some of the fibers from the bypass tracts, illustrating their Purkinje characteristics of coarse myofibrils and a clear perinuclear zone (*arrows*). (All stained with Goldner trichrome. *A*, ×10; *B*, ×25; and *C*, ×160.)

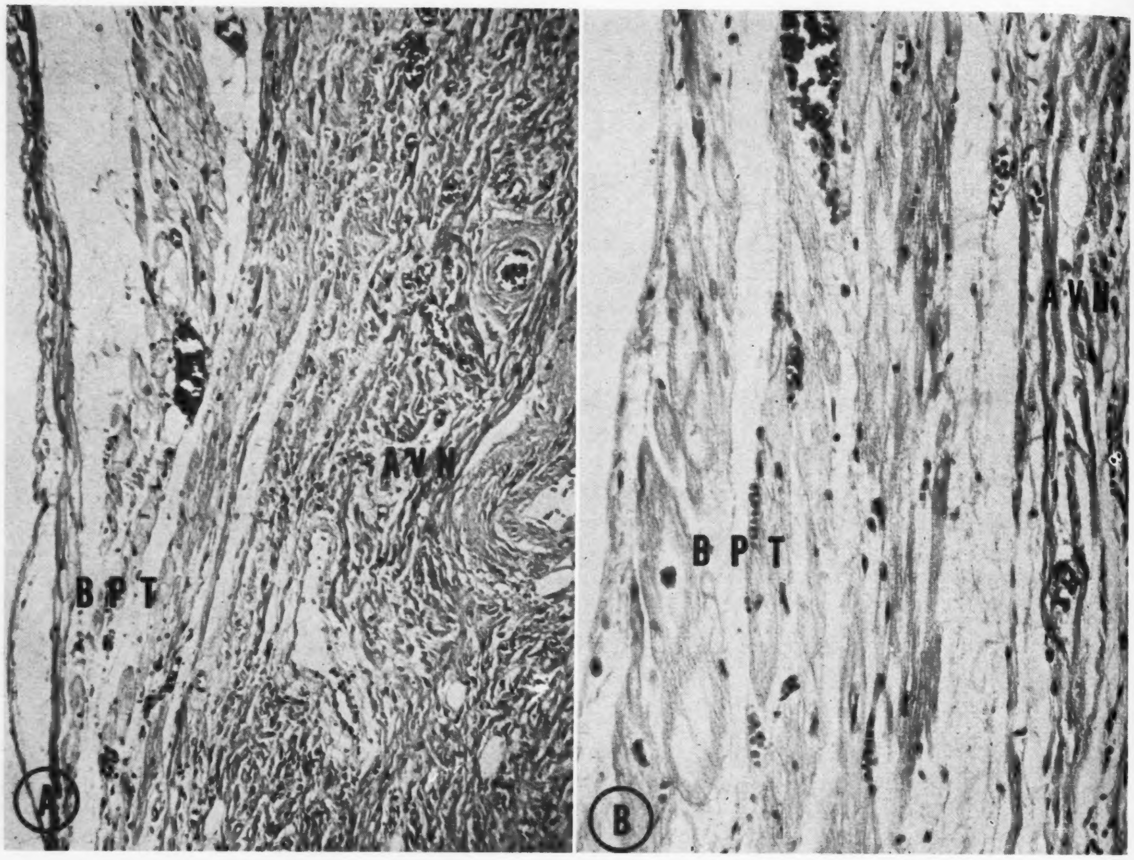

Fig. 6. Two views of the A-V node and bypass tracts from the heart of a 64-year-old man. Orientation in *A* is similar to that in Fig. 5,*A*; this photomicrograph is of the upper portion of the node. In *B* the comparative sizes of the large Purkinje fibers in the bypass tracts and the small fibers in the A-V node are well shown. (Both are stained with Goldner trichrome. *A* ×25; *B* ×64.)

It is widely accepted that rapid conduction occurs in Purkinje fibers[39,40]; whether rapid conduction may also occur in fibers not possessing this morphology is uncertain. Thus, the absence of Purkinje fibers in the right atrial endocardial bypass tracts of some human hearts prevents one from assuming that all these tracts conduct rapidly, but it does not exclude the possibility.

If the bypass tracts do conduct rapidly, as the presence of Purkinje fibers suggests, they are an obvious route by which an impulse may circumvent the A-V node. Such an impulse could re-enter the inferior margin of the node and bypass directly to the A-V bundle. If there is dual conduction in the bundle, such a premature arrival of a bypassing impulse might produce premature excitation of one of the bundle branches, especially the right. However, with current techniques, no morphologic characteristic has been found that suggests dual conduction in the A-V bundle, which, instead, appears to be a uniform sheath of similar fibers. Its morphology does not exclude such a physiologic possibility.

A large number of the hearts in this study were from patients in whom extensive electrocardiographic studies had been made, including electrocardiograms twice daily for as long as 2 weeks. In none of these patients were there any electrocardiographic changes that suggested the Wolff-Parkinson-White phenomenon, although, anatomically, most of them had bypass tracts which contained Purkinje fibers. It is obvious that the presence of such tracts does not mean that they regularly carry an impulse around the A-V node to excite the A-V bundle prematurely. Therefore, it must be assumed that their function of rapid conduction and bypass of the A-V

node, if it exists, is intermittent. This is not incompatible with current electrophysiologic observations.

In their study of the physiology of A-V conduction, Moe and co-workers[18] postulated a dual A-V conduction system, the tracts of which communicated with each other. They proposed that impulse cancellation could occur through these communications, rendering one of the pathways inoperative. This is entirely consonant with the morphology described here; such cancellation conceivably occurs at several points. The first of these is at the posterior margin of the node, where tracts from the interatrial septum and from the Eustachian ridge meet or decussate. The second is at the junction of the bypass tracts with the inferior margin of the node. However, to presume cancellation at the latter point, it would be necessary for the impulses passing through the node and through the bypass tract to travel at approximately the same speed. Otherwise, more rapid conduction in the bypass tract would produce excitation of the A-V bundle before the impulse through the A-V node could arrive there; in such a case simultaneous

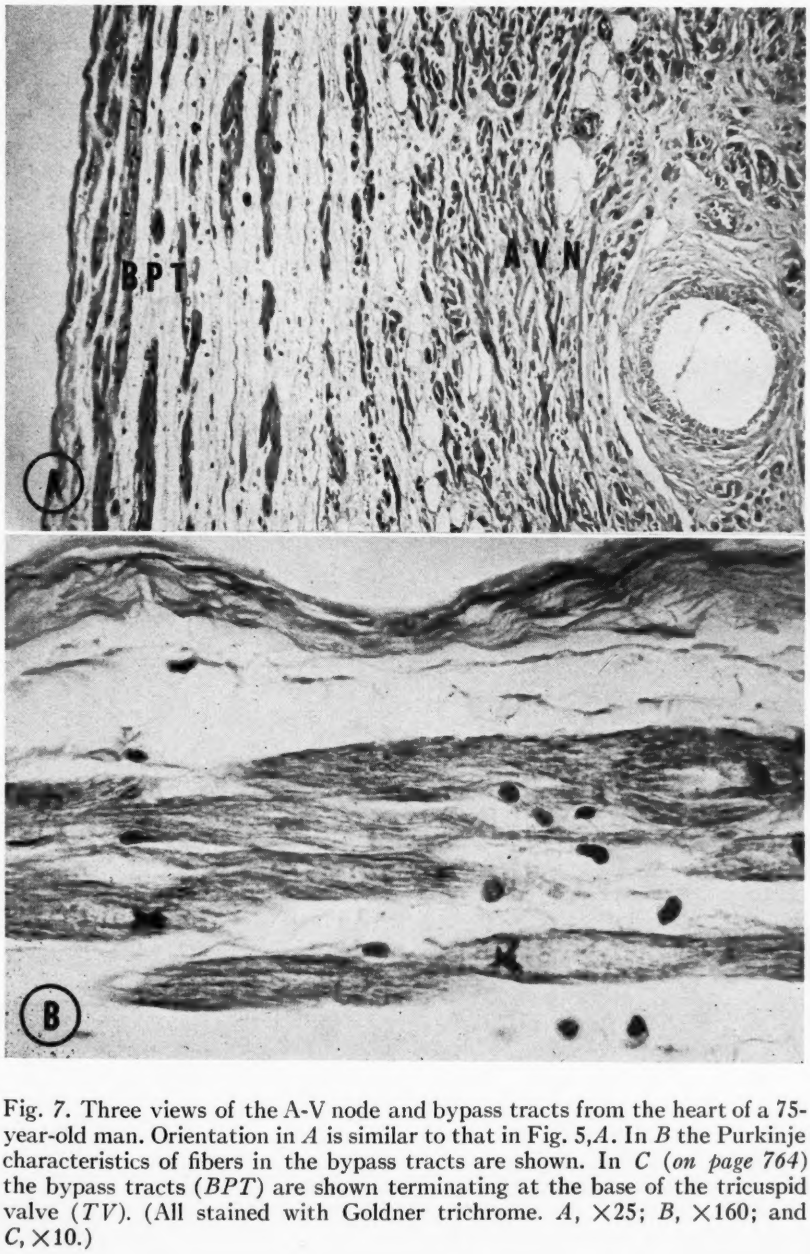

Fig. 7. Three views of the A-V node and bypass tracts from the heart of a 75-year-old man. Orientation in *A* is similar to that in Fig. 5,*A*. In *B* the Purkinje characteristics of fibers in the bypass tracts are shown. In *C* (*on page 764*) the bypass tracts (*BPT*) are shown terminating at the base of the tricuspid valve (*TV*). (All stained with Goldner trichrome. *A*, ×25; *B*, ×160; and *C*, ×10.)

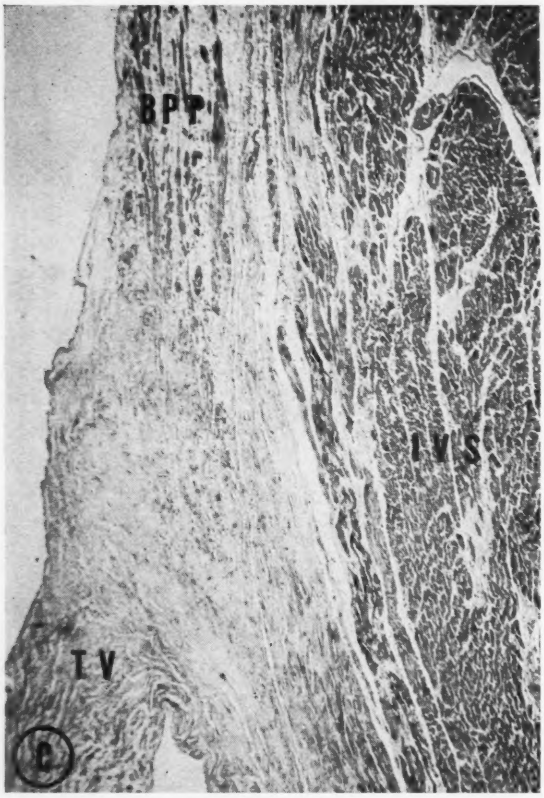

Fig. 7,C. (*For legend see page 763.*)

spread of the impulse both down the A-V bundle and back up the A-V node might cause retrograde cancellation in the latter. Finally, in some A-V nodes there is an outer layer of relatively straight non-anastomosing fibers; an impulse traveling in them might reach the inferior margin of the node at the same time that an impulse via the bypass tracts did, which would produce cancellation.

Although numerous observers have documented a delay in A-V conduction which occurs in the region of the A-V node,[5,14,18,20,24,27] there is some debate whether this occurs in the node or at the atrionodal junction. Morphologically, there is nothing about the tracts in the interatrial septum or Eustachian ridge near the A-V node which would suggest decelerated conduction. The structure of the node, however, suggests a mechanism of delay there. If one can presume that impulse cancellation may occur when two juxtanodal tracts meet,[18] the same type of cancellation may occur within the node.

With the exception of a few relatively straight fibers in the outer layer of the node, all the other fibers are short and ramify to anastomose with each other profusely. An impulse entering such a labyrinth of pathways must be divided and rerouted many times, even if conducted without interruption. If a divided impulse follows fibers which later rejoin, cancellation may occur. This circuitous pathway of an impulse wandering within the node is supported by the observations of Pruitt and Essex,[20] who noted a broad "hump" in electrograms recorded from the node, in contrast to a sharp biphasic spike in those from the A-V bundle. Similar wide

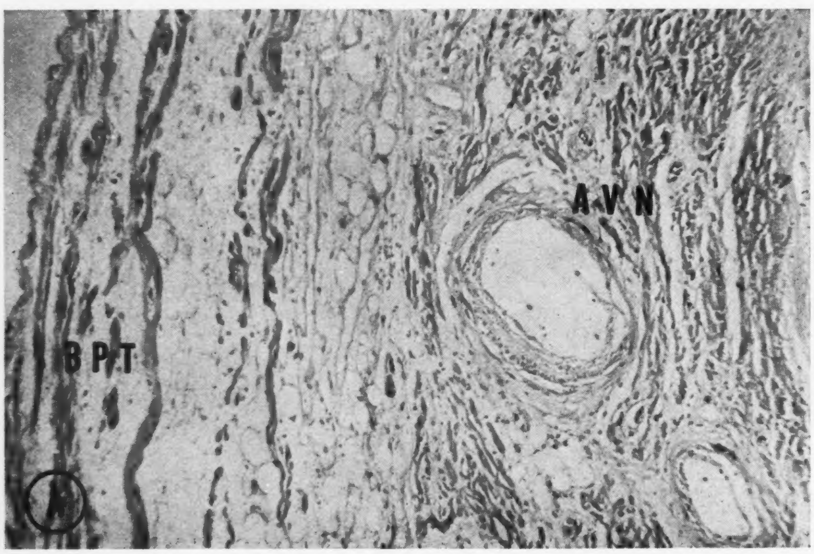

Fig. 8,A. (*For part B and legend see top of page 765.*)

Fig. *8*. Two views of the A-V node and bypass tracts from the heart of a 53-year-old man. Orientation is similar to that in Fig. 5,*A*. A Purkinje fiber from the bypass tract is shown in *B*. (Both stained with Goldner trichrome. *A*, ×25; and *B*, ×160.)

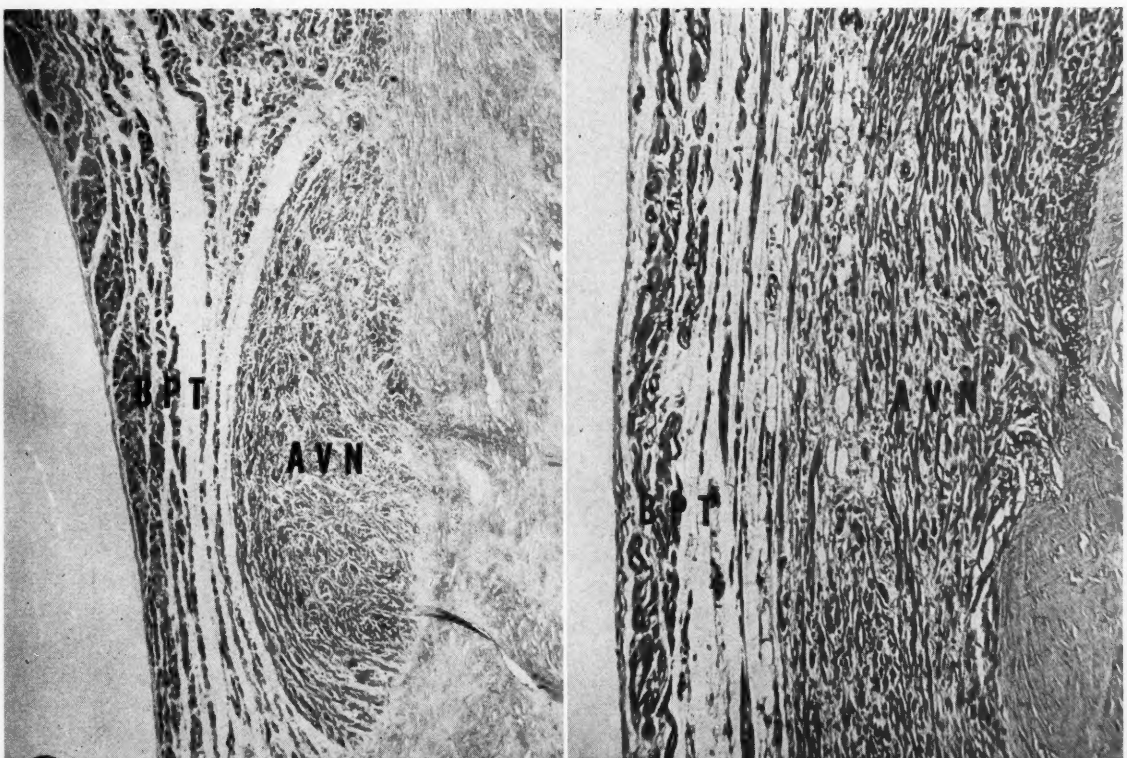

Fig. *9*. Views of the A-V node and bypass tracts from two different hearts. *A* is from the heart of a 29-year-old woman, and *B* is from the heart of a 44-year-old woman. The relationships of the bypass tracts and the A-V node are well shown in *A*. In *B* some of the bypass tract fibers are cut transversely and others obliquely or longitudinally; this variation in course is not unusual. Also, in *B* a few of the fibers in the middle of the node seem to be descending directly instead of arborizing frequently; this is unusual. (Both stained with Goldner trichrome. *A*, ×10; and *B*, ×25.)

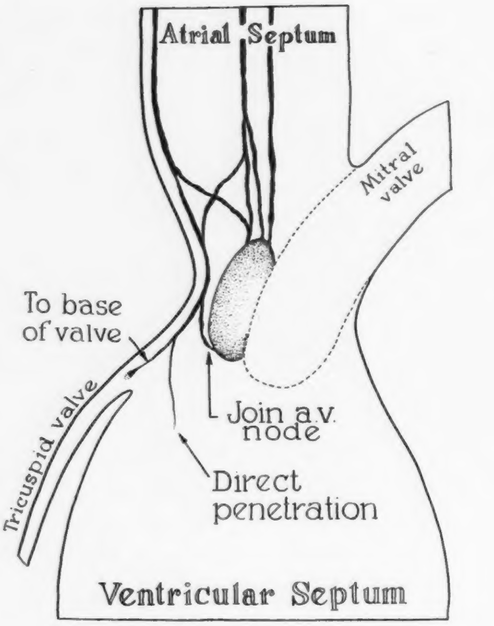

Fig. *10*. A drawing from a representative cross section of a normal human A-V node, with its relationships to the bypass tracts. Orientation is the same as in Figs. *1*, *2*, and *11*.

complexes have been recorded from the A-V node by Scher and his colleagues.[27]

Such a slowing of the normal impulse when it arrives in the A-V node, with the possibility of a rapid bypass tract parallel to the node, is the reverse of the suggested dual system of Moe and his colleagues.[18] In their proposal it was the normal pathway which conducted rapidly, whereas the conduction in the bypass tract was delayed. Because of a postulated delay in the bypass tract, they were unable to employ their hypothesis to explain the Wolff - Parkinson - White syndrome, although they could explain reciprocal rhythm and paroxysmal supraventricular tachycardia. By means of their same reasoning, the present findings on the morphology of the node and its environs can be used to explain all three of these electrocardiographic phenomena, since the present findings suggest that conduction would usually be more rapid in the bypass tract than in the A-V node.

Additionally, if conduction delay does occur within the node because of multiple cancellation, it is possible to explain both accelerated and delayed A-V conduction through an injured A-V node. If the injury is focal, normal cancellation or deviation of the impulse in the interconnecting fibers may be prevented, and conduction may occur in a straighter, more direct route. This is illustrated by the finding of both shortened and prolonged A-V conduction in acute posterior myocardial infarction. The supply of blood to the crux of the heart, which is compromised in true posterior infarctions, is also the supply of blood to the human A-V node.[41,42]

In the same manner, focal lesions within the node can establish a dual conduction system, even without consideration of the bypass tracts. It has been postulated above that the normal delay in A-V conduction occurs within the A-V node and is caused by a multiple cancellation effect. If focal disease within the node involves predominantly one half, the other half would still be subject to the normal amount of this interference in conduction, whereas the diseased half may have a sufficient number of interconnections removed to permit a more direct conduction of an impulse (Fig. 14). From this postulated basic division of conduction within the labyrinthine internal structure of the pathologic node, one may construct explanations for reciprocal rhythm and the Wolff-Parkinson-White phenomenon in the same manner as with the dual conduction system hypothesis of Moe and others.[18] It is not so strange that an impulse in the normal A-V

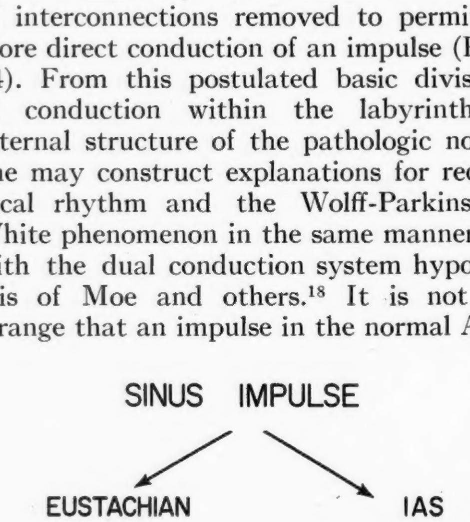

Fig. *11*. A schematic chart indicating the pathways which an impulse may follow from the sinus node to the A-V bundle, including the alternative route bypassing the A-V node. This chart supplements the data presented in Figs. *1*, *2*, and *10*.

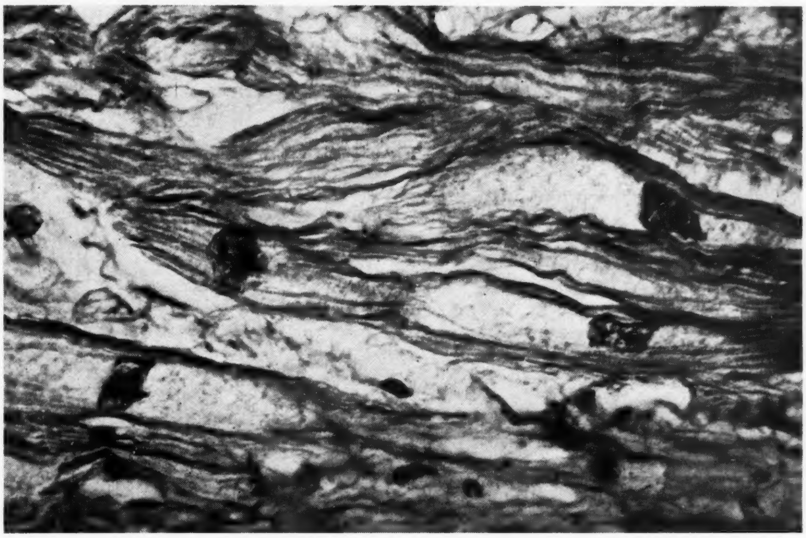

Fig. *12*. A group of Purkinje fibers from the subendocardium of the Eustachian ridge, depicting the classic characteristics of these fibers. Compare to the Purkinje fibers shown from the bypass tracts in the preceding figures. (Goldner trichrome stain, ×160.)

node sometimes becomes delayed or accelerated, but that it is normally transmitted with such regularity and consistency.

Although the present findings do not exclude the possibility of other mechanisms of production of the Wolff-Parkinson-White syndrome,[43] for example, conduction through a bundle of Kent,[44,45] they make it unnecessary to employ such an explanation. It is significant that Purkinje fibers have not been described in instances in which a Kent bundle was identified; the bundle has always consisted of ordinary myocardium.[46-52] Even though fibers which have the appearance of ordinary myocardium may be capable of rapid conduction (as in the human A-V bundle), that possibility has never been proved in man. Evidence from electrocardiographic and vectorial studies is at the very best, quite indirect. It would lend support to the bundle-of-Kent theory if someone would demonstrate Purkinje fibers in a bundle of Kent, since there is good evidence that Purkinje fibers conduct at a rapid rate.

If electrophysiologic studies confirm that the bypass tracts described here actually do operate as an alternate A-V conduction system, then additional considerations will be necessary in regard to the exact function of the A-V node. The suggestion has already been made that it may only be an alternate pacemaker which otherwise has no function.[18] The suggestion has also been made that it is an electronic oscillator which feeds impulses into the A-V bundle at the same rate as does a neighboring dominant oscillator, the sinus node.[7] These and similar theories will require more careful examination.

Certain phylogenetic considerations lend credibility to the significance and function of these human bypass tracts. In the Hunterian Lecture of 1942, Davies[53] presented his results of a study of the conducting system of vertebrate and avian hearts. Both Davies[53] and Sir Arthur Keith[54] had long been interested in the conduction system of birds because of certain functional requirements due to their rapid heart rate; the average heart rate of a canary is 1,000 beats per minute. The tricuspid valve, which is a delicate fibrous structure in mammals, is a strong muscular ring in birds. Because of the rapid ventricular rate in the bird, it is necessary for the tricuspid valve to close actively by muscular contraction, rather than passively, as in the mammal, in order to prevent retrograde regurgitation of ventricular blood. For this to happen, there must be a more rapid conduction of the sinus impulse to the muscular tricuspid ring than to the

Fig. 13. Photomicrograph of the lower A-V node and upper interventricular septum from the heart of an infant. Some of the bypass tract fibers continue directly into the septum (*arrow*). Although only a few hearts from infants were studied, this finding does not seem to be uncommon in these hearts, suggesting that fibrous demarcation between atria and ventricles is more distinct in the adult heart. (Goldner trichrome stain, ×25.)

ventricular myocardium, and it was the pathway of this impulse which Davies defined. Although there are some differences between the disposition of this bypass tract in birds and that in man (as there are also differences in the topography of the A-V node), there are also basic similarities. In particular, the termination of some of the bypass tract fibers at the base of the tricuspid valve in man are suggestively similar. What the function of these fibers near the tricuspid valve is in man can only be conjectured at the present time. If they carry impulses at all, one must even consider whether they carry impulses to or away from the tricuspid ring.

In addition to Davies' observations in birds, de Carvalho and de Almeida[5] have described a somewhat similar structure in the rabbit, which they designate the *sinoatrial ring bundle*. They believe that this structure can undertake pacemaker functions, and emphasize its regular termination over the atrial border of the atrionodal junction. Speculating that this ring was a remnant of the embryonic A-V ring, they suggest that it may contribute certain delaying properties to A-V conduction. Whether this reasoning may be applied to A-V nodal electrophysiology in man remains to be determined. The frequency of the Wolff-Parkinson-White phenomenon in Ebstein's anomaly[11] suggests that this may be a human analogy.

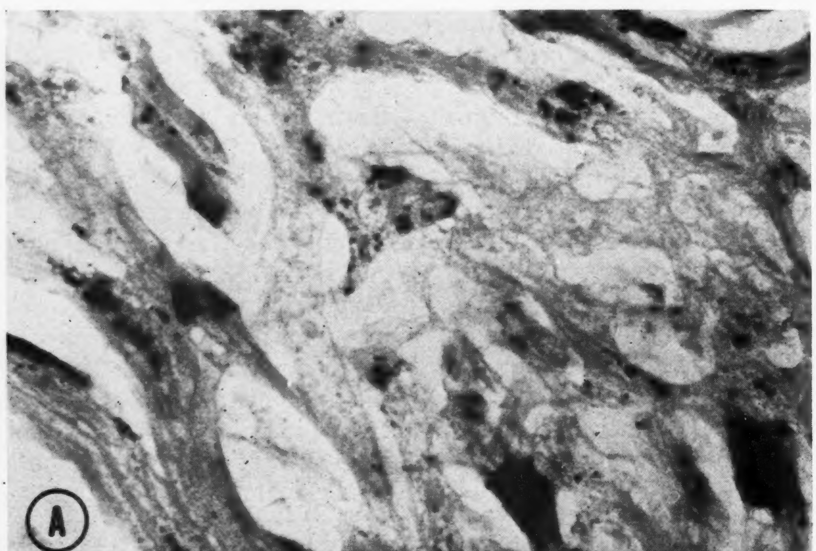

Fig. 14,A. (*For parts B and C and legend see opposite page.*)

In the dog a large mass of fibers is present between the A-V node and the right atrial endocardium (Fig. 15). Whether these function as a bypass tract is unknown. Most electrographic studies in this region of canine hearts have employed either plunge electrodes inserted into the A-V node or surface electrodes sutured directly to the right atrial endocardium. Both of these methods may injure the bypass tracts of the dog, if they exist. Studies employing nontraumatic electrodes are needed to record electrograms from the endocardium over the A-V node which can be compared with simultaneous records obtained from within the node (perhaps by means of a plunge electrode placed from the left atrial side). These should help elucidate the problem of whether impulses travel in a bypass tract, and what the relation of such conduction is to electrical activity in the A-V node.

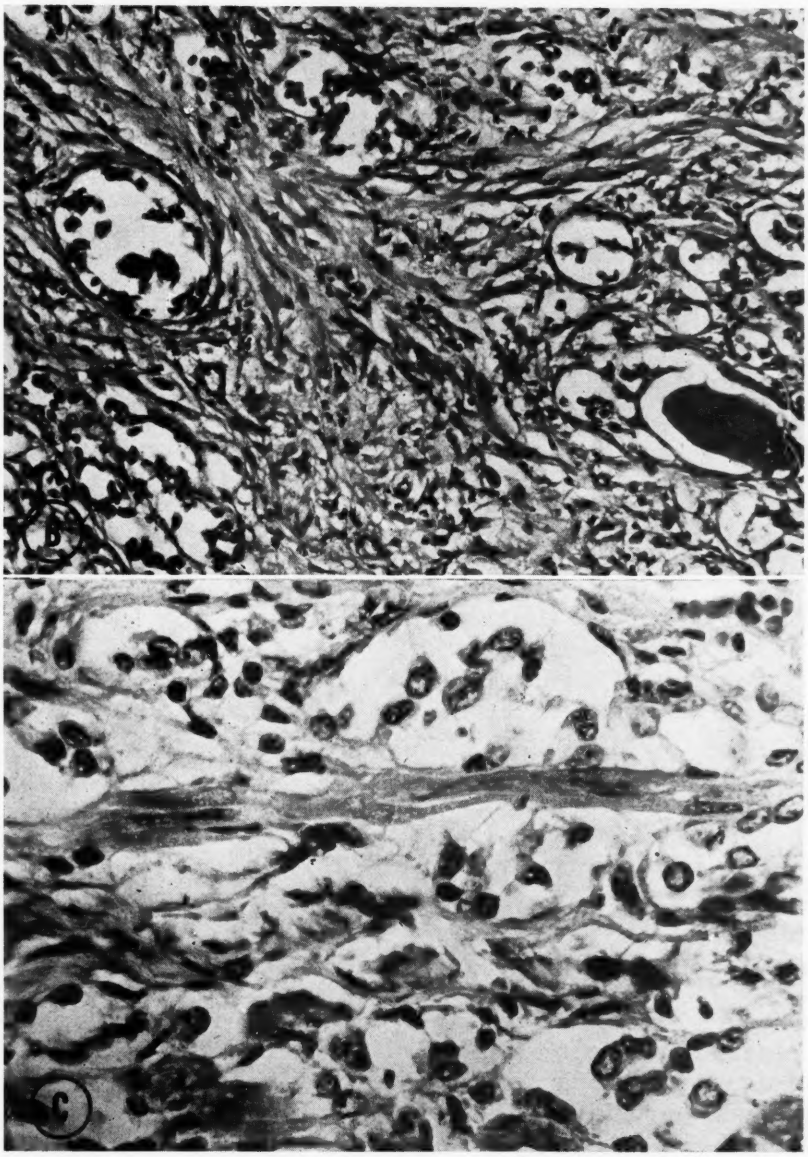

Fig. *14*. Photomicrographs of the pathologic A-V nodes from two patients with (*A*) hemachromatosis and (*B* and *C*) hypernephroma metastatic to the A-V node. The disruption of normal interconnection of fibers is apparent. (*A*, Iron reaction counterstained with safranin, ×205; *B*, PAS, ×64; *C*, Goldner trichrome, ×160.)

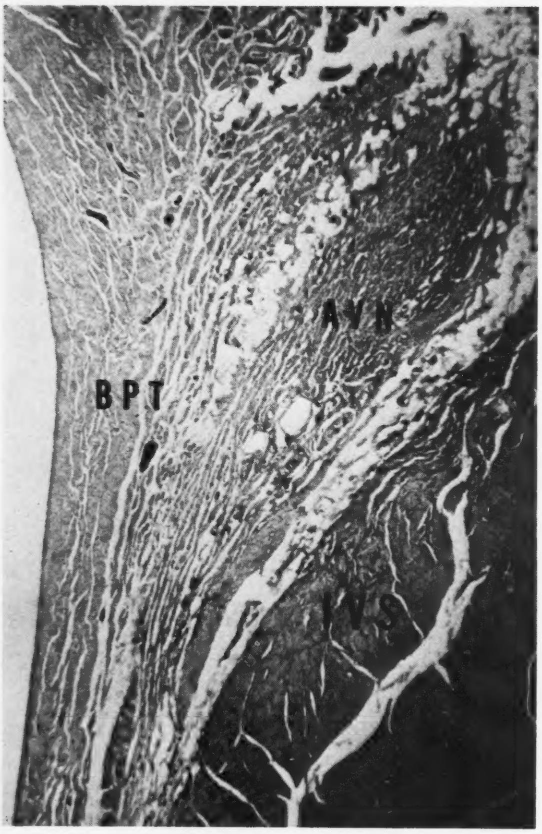

Fig. *15*. Photomicrograph of the A-V node and bypass tract in a dog. Orientation is similar to the views of the human hearts. (Goldner trichrome stain, ×10.)

Summary

The morphology of the A-V node and its environs in man was studied in 81 hearts. Between the node and the endocardium of the right atrium are Purkinje fibers which may function as bypass tracts, allowing an impulse from the sinus node to circumvent the A-V node. This alternate pathway lends support to recent electrophysiologic studies which have suggested such a dual conduction system.

Because of the profuse interconnections of the normal A-V node fibers, the suggestion is made that the slight delay in impulse conduction observed in this region may be a multiple cancellation effect within the node. The same morphologic feature may conceivably combine with focal nodal disease to produce dual conduction inside the A-V node.

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Electrocardiographic alterations after neurosurgical procedures

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The influence of the central nervous system on the function of other systems has been the subject of extensive investigation. In this respect the cardiovascular system has received considerable attention, at both the experimental and the clinical levels. In particular, electrocardiographic changes have been reported in a variety of abnormal cerebral states, especially after cerebrovascular accidents.[1-4] Electrocardiographic changes have been observed in the course of experimental stimulation of various cortical and subcortical areas of the brain,[5,6] and in the course of experimental trauma and cerebral compression.[7-9]

Reports have appeared concerning the electrocardiographic changes during various operative and diagnostic neurosurgical procedures.[10-13] The changes recorded in these clinical studies relate mainly to changes in blood pressure and disturbances in cardiac rhythm.

During the last 2 years we have been impressed with the frequent and striking electrocardiographic changes which occur after diagnostic, operative, and combined neurosurgical procedures. In contrast with previously reported observations, our findings consisted mainly of prolongation of Q-T and alterations in the T and U waves. Arrhythmias were not a common finding in this study. We report these observations in the hope that they may help elucidate the complex regulatory mechanism of the central nervous system on the function of the cardiovascular system.

Material and methods

A total of 37 consecutive patients were studied during the period from November, 1958, to May, 1960. The procedures performed on these patients are listed in Table II.

Each patient had a complete 12-lead electrocardiogram preoperatively on the day preceding the neurosurgical procedure. Postoperative tracings were taken on an average of 2 to 4 hours after completion of the procedure, and, in most instances, for several days subsequently. In a few subjects, stabilization of the electrocardiogram or return to the preoperative state did not occur for several weeks. These patients were followed up by the taking of frequent tracings. A notation was made concerning the state of nutrition of each patient prior to hospitalization, occurrence of vomiting, presence or history of cardiovascular disease, and administration of drugs known to alter the electrocardiogram. Serum sodium and potassium were determined by the flame photometric method.[14] Serum chloride was determined by the

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titration method.[15] Calcium was determined by the Clark-Collip method, and phosphorus, by the Fiske-Subbarrow method.[16,17] The range of normal for this laboratory is as follows: chloride, 94 to 108 mEq. per liter; sodium, 134 to 144 mEq. per liter; potassium, 3.5 to 5.3 mEq. per liter; calcium, 9 to 11.5 mg. per cent; and phosphorus 2.5 to 4.5 mg. per cent.

The ventriculograms and pneumoencephalograms were obtained by the replacement method, employing local anesthesia for the ventriculograms and general anesthesia for the pneumoencephalograms.

We studied each electrocardiogram separately. The degree of prolongation of Q-T was determined for the preoperative and for each of the postoperative tracings. This was accomplished by comparing the actual Q-T interval with the predicted Q-T interval as determined by the formula of Bazett.[18] The Q-T interval was obtained from the precordial leads since Leads V_2, V_3, and V_4 gave the clearest demarcation of the end of the T wave. At times the U wave merged with the terminal limb of the T wave. In these cases no attempt was made to separate the Q-T interval from the Q-U interval. The Q-T interval was considered to be significantly prolonged when its duration exceeded 20 per cent of its predicted value.

Table I summarizes pertinent clinical information concerning each of the subjects. The preoperative clinical cardiac evaluation, including determinations of blood pressure, electrocardiogram, and chest x-ray film, was normal for the entire group except for 3 patients. Patients 17 and 35 had hypertension and cardiac enlargement; Patient 21 had coronary artery disease. These 3 patients had abnormal electrocardiograms.

Results

The ages of our patients ranged from 6 weeks to 68 years, with an average of 38.7 years. There were 17 female and 20 male patients.

Table II tabulates the incidence of the electrocardiographic alterations after the various neurosurgical procedures.

The three most prominent and frequent changes consisted of prolongation of the Q-T interval, alterations in the T wave, and prominence of the U waves. There were 17 patients who showed Q-T prolongation as determined from the formula of Bazett. The increase ranged from 5.3 to 107 per cent, with an average increase for the entire group of 42.6 per cent. Q-T prolongation of a significant degree (20 per cent or more) occurred in 15 patients, for an incidence of 41 per cent. Of the various procedures, Q-T prolongation was observed most frequently in those patients who were undergoing a craniotomy with or without ventriculography. Of 12 such patients, significant prolongation was observed in 7, for an incidence of 60 per cent. The measured Q-T interval exceeded the predicted Q-T interval in the preprocedural electrocardiograms by 20 per cent in only 2 patients. These 2 patients showed additional prolongation of a significant degree after the neurosurgical procedure.

The T-wave alterations ranged from a significant decrease in amplitude of the T wave to partial inversion. This occurred in 28 patients, for an incidence of 76 per cent. The altered T waves were frequently widened, which suggested incorporation of the U wave. It is to be noted that 3 patients had abnormalities of the T waves before the procedure. In Patient 35 the T waves were originally inverted and became upright after pneumoventriculography. The inverted T waves in Patient 21 became more deeply inverted after craniotomy. Patient 17 originally showed flattening of the T waves, and there was no change after pneumoventriculography. Patient 25 had a normal electrocardiogram and, after a craniotomy for metastatic malignancy, developed ECG changes compatible with a subendocardial myocardial infarction.

Prominence of the U wave was not present in any of the tracings taken preoperatively, and developed in 18 patients after the procedure, an incidence of 48.7 per cent. It was particularly prevalent after pneumoencephalography and craniotomies.

The fourth most frequent finding was a pronounced sinus arrhythmia which occurred in over one third of the patients who underwent ventriculography and pneumoencephalography.

Other alterations in the electrocardiograms were not a prominent finding in our cases and are listed in Table II.

Table I. Clinical data

Patient number	Procedure	Age (yr.) sex	Final diagnosis	Neurological findings	Spinal fluids	Electrolytes		Cardiovascular status
						Preop.	Postop.	
1.	Pneumoencephalography	16, M	Convulsive disorder	None	Normal			Normal
2.	Pneumoencephalography	28, F	Anxiety reaction	None	Normal			Normal
3.	Pneumoencephalography	17, F	Epilepsy	Ataxia	Normal			Normal
4.	Ventriculography	49, M	Metastatic carcinoma to brain	Hemiparesis, left; nerve palsy, left, 5, 6, 7	Normal			Normal
5.	Ventriculography	6 wk., M	Porencephalic cyst	Hydrocephalus	Increased protein (254 mg. %), increased cells	Ca 10* P 3.2	CO_2† 23 Cl 92 Na 135 K 3.9	Normal
6.	Ventriculography and occipitoparietal craniotomy, left	64, F	Occipital lobe glioblastoma multiforme, left	Aphasia; nerve palsy, right, sixth	Increased pressure	CO_2 24 Cl 101 Na 138 K 4.1	CO_2 27 Cl 102 Na 137 K 4.0	Normal
7.	Ventriculography	40, F	Brain tumor suspect	Headaches, marked papilledema	Increased pressure	CO_2 24 Cl 105 Na 137 K 4.6 Ca 10.9	CO_2 21 Cl 102 Na 140 K 4.1	Normal
8.	Pneumoencephalography	27, M	Epilepsy	None	Normal			Normal
9.	Pneumoencephalography	41, F	Histamine sensitivity	Vertigo, nystagmus	Normal			Normal
10.	Frontotemporal craniotomy, right	39, M	Chromophobe pituitary adenoma	Hemianopsia	Not studied	CO_2 24 Na 140 Cl 99 K 4.8	CO_2 25 Na 140 Cl 96 K 4.8	Normal

11.	Pneumoencephalography	13, F	Anxiety reaction, brain tumor suspect	Slight ataxia	Normal		CO_2 17 Na 130 Cl 97 K 3.8	Normal
12.	Suboccipital craniotomy	5, M	Cystic astrocytoma, left cerebellar	Papilledema, ataxia	Increased pressure		CO_2 26 Cl 95 Na 132 K 4.5	Normal
13.	Frontal craniotomy, right	56, F	Old arachnoiditis of chiasm	Blindness, optic atrophy	Not studied			Normal
14.	Pneumoencephalography	31, M	Brain tumor suspect, internal carotid insufficiency	Numbness, weakness of left arm	Protein 91 mg. %; pressure 220 mm.			Normal
15.	Ventriculography and parietal craniotomy, right	43, M	Brain disease metastatic from lung	Positive Babinski, left foot; papilledema	Increased pressure	CO_2 22 Cl 98 Na 130 K 4.6	CO_2 26 Cl 93 Na 131 K 4.6	Normal
16.	Ventriculography	64, M	Cerebral arteriosclerosis	Headaches	Normal			Normal
17.	Pneumoventriculography	34, M	Hypertensive encephalopathy	Ataxia, positive Romberg	Normal			Suspiciously positive Master's test; blood pressure 170/100 mm. Hg
18.	Pneumoencephalography	39, F	Idiopathic epilepsy	Ataxia, positive Romberg	Normal			Normal
19.	Pneumoencephalography	15, F	Convulsive state	None	Normal	CO_2 24 Cl 99 Na 140 K 3.7	CO_2 23 Cl 98 Na 138 K 3.4	Normal
20.	Ventriculography	36, F	Brain tumor suspect	None	Normal			Normal

*Ca and P were recorded in mg. per cent.
†CO_2, Cl, Na, and K were recorded in mEq. per liter.
Table I is concluded on pages 776 and 777.

Table I. *Clinical data*—Cont'd

Patient number	*Procedure*	*Age (yr.) sex*	*Final diagnosis*	*Neurological findings*	*Spinal fluids*	*Electrolytes*		*Cardiovascular status*
						Preop.	*Postop.*	
21.	Frontoparietal craniotomy, left	53, M	Frontal lobe glioma, left	Babinski, left; central facial weakness	Increased pressure, 400 mm.		CO_2 30 Cl 92 Na 141 K 3.6 Ca 9.7 P 4.02	Inverted T waves
22.	Ventriculography	54, F	Cerebral atrophy	Bilateral hyperreflexia	Protein, 52 mg. %			Normal
23.	Ventriculography and suboccipital craniotomy	58, M	Metastasis to brain from pulmonary neoplasm	Vertigo, poor coordination, positive Romberg	Negative	CO_2 23 Cl 103 Na 135 K 4.0	CO_2 25 Cl 98 Na 135 K 3.5	Normal
24.	Ventriculography and temporoparietal craniotomy, right	57, M	Parietal glioblastoma multiforme, right	Papilledema; hemiparesis, left	Not studied		CO_2 30 Cl 94 Na 135 K 3.8	Normal
25.	Frontoparietal craniotomy, right	50, M	Metastasis to brain from pulmonary neoplasm	Bell's palsy, right; hemiparesis, left	Not studied		CO_2 20 Cl 98 Na 129 K 4.9	After craniotomy, developed anterolateral subendocardial infarction
26.	Pneumoencephalography	18, F	Post-traumatic cephalalgia	Negative	Normal		CO_2 24 Cl 99 Na 142 K 4.7	Normal
27.	Ventriculography	33, M	Headaches after craniotomy	Severe headache	Pressure, 210 mm.	CO_2 23 Cl 103 Na 135 K 3.6		Normal
28.	Ventriculography	56, M	Arachnoiditis of posterior fossa	Papilledema scotomata	Increased pressure			Normal

29.	Ventriculography	68, M	Cortical atrophy	Motor loss, bilateral; disorientation	Negative			Normal
30.	Pneumoencephalography	6, F	Idiopathic epilepsy	None	Negative	Ca 10		Normal
31.	Frontotemporal craniotomy, left	38, F	Sphenoid ridge meningioma, recurrent	Hemiparesis, right	Not studied			Normal
32.	Ventriculography	55, M	Cortical atrophy	Hemiparesis, right; disorientation	Increased protein, 87 mg. %	CO_2 19 Cl 105 Na 135 K 4.4	CO_2 16 Cl 98 Na 132 K 3.4	Normal
33.	Pneumoencephalography	56, M	Temporal lobe tumor, left	Hemiparesis, right	Normal	CO_2 24 Cl 101 Na 140 K 4.1	CO_2 23 Cl 101 Na 136 K 3.9	Normal
34.	Frontoparietal craniotomy, left	42, F	Frontal lobe dermoid cyst,	Negative	Normal	CO_2 29 Cl 94 Na 135 K 4.4	CO_2 26 Cl 94 Na 137 K 4.2	Normal
35.	Pneumoventriculography	42, F	Hypertensive cerebrovascular disease	Hemiparesis, right dysarthria	Normal	CO_2 21 Cl 102 Na 142 K 4.0	CO_2 20 Cl 104 Na 139 K 4.1 P 3.4 Ca 10	Large heart; hypertension, 240/170 mm. Hg; T-wave inversions
36.	Pneumoencephalography	39, F	Occipitoparietal arachnoiditis, right	Headaches, convulsive state	Normal		CO_2 27 Cl 93 Na 132 K 4.0 Ca 10.9 P 3.25	Complained of chest pain with radiation to left arm
37.	Ventriculography and temporal craniotomy, left	56, M	Temporal lobe spongioblastoma, left	Hemiparesis, right	Not studied	CO_2 24 Cl 100 Na 139 K 4.2	CO_2 24 Cl 101 Na 140 K 3.9	Normal

Table II. *Incidence of ECG alterations after various neurosurgical procedures*

	Preoperative	*Pneumoencephalography*	*Ventriculography*	*Pneumoventriculography*	*Ventriculo-craniotomy*	*Craniotomy*	*Total*	*Per cent*
Number of patients	37	13	10	2	5	7	37	100.0
Alterations in T wave	3	8	8	2	4	6	28	75.6
Prominent U wave	0	7	2	1	4	4	18	48.6
Prolongation of Q-T interval	2	6	4	0	4	3	17	45.9
Sinus arrhythmia	0	5	3	0	1	0	9	24.3
Alterations in P wave	1	2	1	0	2	1	6	16.2
Changes in QRS electrical axis	0	1	2	1	1	1	6	16.2
Alteration in S-T segment	0	1	1	0	2	2	6	16.2
Sinus bradycardia	0	2	2	0	1	0	5	13.5
Sinus tachycardia	0	0	1	0	4	0	5	13.5
Extrasystoles	0	3	2	0	0	0	5	13.5
Large upright T wave	0	1	0	0	1	0	2	5.4
Low QRS voltage	0	0	0	0	1	0	2	5.4
Coronary sinus rhythm	0	1	0	0	0	0	1	2.7

The duration of the electrocardiographic changes ranged from 2 to 6 days; in a few patients the alterations persisted for a longer period of time.

Examples of the chief electrocardiographic abnormalities are shown in Figs. 1 to 4.

Discussion

In contrast to the previously reported alterations in the electrocardiogram after cerebrovascular accidents and surgical removal of brain tissue,[1-4,10] the analysis of the changes in patients who underwent air studies provided a less complex and more physiologically intact setting for studying cerebrocardiac relationships.

In considering the possible cause or causes of the electrocardiographic changes observed in our material, several possibilities have to be considered. The electrocardiographic changes observed simulate alterations frequently associated with disturbances of electrolyte balance. Electrolyte disturbances have been implicated by some workers as a possible explanation for the electrocardiographic changes which follow cerebrovascular accidents.[2] Other investigators have presented evidence against this concept.[3] In reviewing our

material we were unable to demonstrate any correlation between the depletion of serum electrolytes and the changes in the electrocardiogram. The possibility, however, that some of the changes in the electrocardiogram are a reflection of alterations in electrolytes at the cellular level cannot be discarded.

Some authors have attributed the electrocardiographic changes which follow cerebrovascular accidents to primary myocardial alterations of ischemic origin involving the subendocardial layers of the myocardium and frequently engrafted on previously existing coronary artery disease.[4,19] This explanation is much less

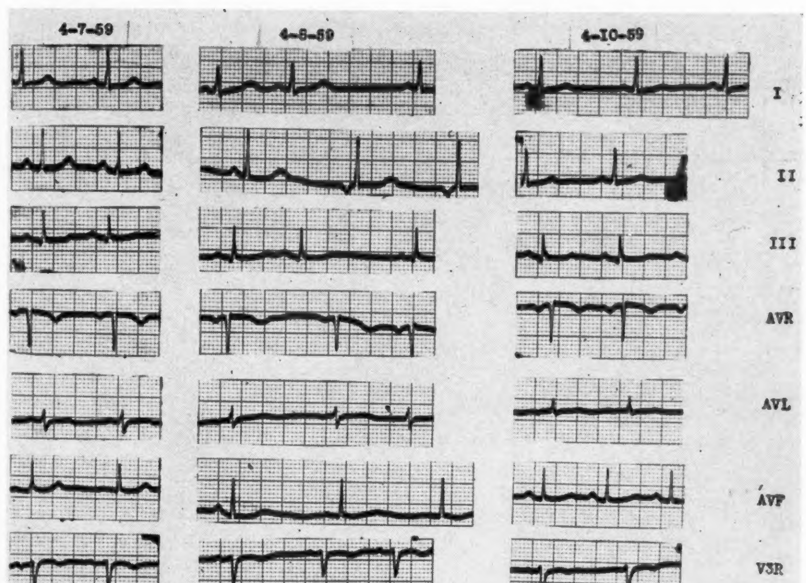

Fig. *1.* Patient 19. The preoperative tracing of April 7, 1959, is normal. The second tracing was taken 2 hours after completion of the pneumoencephalogram. Note the marked prolongation of the Q-T interval (61.7 per cent), the inclusion of the U wave on the descending limb of the widened T wave, sinus arrhythmia, coronary sinus rhythm in Lead II, and an extrasystole in Lead V_1. The tracing of April 10 has returned to normal. The preoperative and postoperative serum electrolytes were normal.

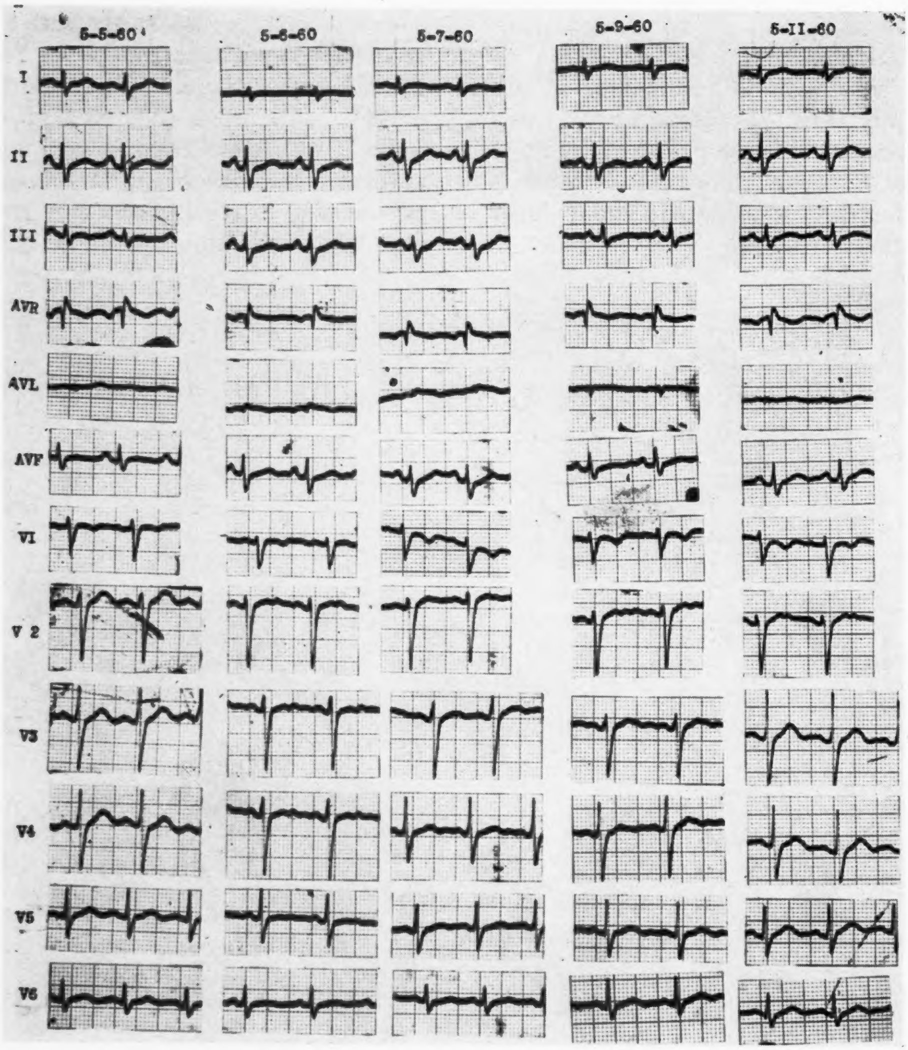

Fig. *2*. Patient 34. The preoperative electrocardiogram taken on May 5, 1960, is normal. On May 6, 2 hours after a craniotomy for partial removal of a left frontal lobe dermoid cyst, the electrocardiogram revealed marked diminution in the amplitude and notching of the T waves in the precordial leads. The tracing returned to normal by the fifth postoperative day. Preoperative and postoperative serum electrolytes were normal.

applicable to our material, when we consider the age difference of our patients as compared with the usual population suffering from cerebrovascular accidents. More than half of our patients were below the age of 40. The great majority of our patients had no electrocardiographic or clinical evidence of heart disease. Furthermore, at autopsy the heart was reported to be normal in patients who showed electrocardiographic patterns suggestive of myocardial infarction in association with subarachnoid hemorrhage.[4]

The third possible mechanism is that these changes in the electrocardiogram are a manifestation of altered cerebral function incident to the various neurosurgical procedures. The control exerted by the central nervous system on the various functions of the cardiovascular apparatus is indeed a very complex subject. Most of the studies in this area have been concerned mainly with stimulation of various cortical and subcortical areas and observations of readily detectable changes, such as blood pressure and arrhythmias.[5,6] Of all the subcortical areas the hypothalamus has been studied most extensively, and it appears to have a definite relation to cardiac function. These studies, however, confirm

previous work with regard to striking alterations in rhythm and in the individual waves of the electrocardiogram during hypothalamic stimulation, especially of the lateral and posterior portions. Some investigators have been able to reproduce cardiac changes which simulate the physiologic response to exercise by stimulation of various areas of the hypothalamus.[20] This work suggests that the myocardial responses may, under certain circumstances, be under neural control.

Other studies that may have some bearing on our results and observations relate to stimulation of the vagus nerve and its effects on the myocardium. There is some evidence in experimental animals that excessive vagal stimulation may in itself

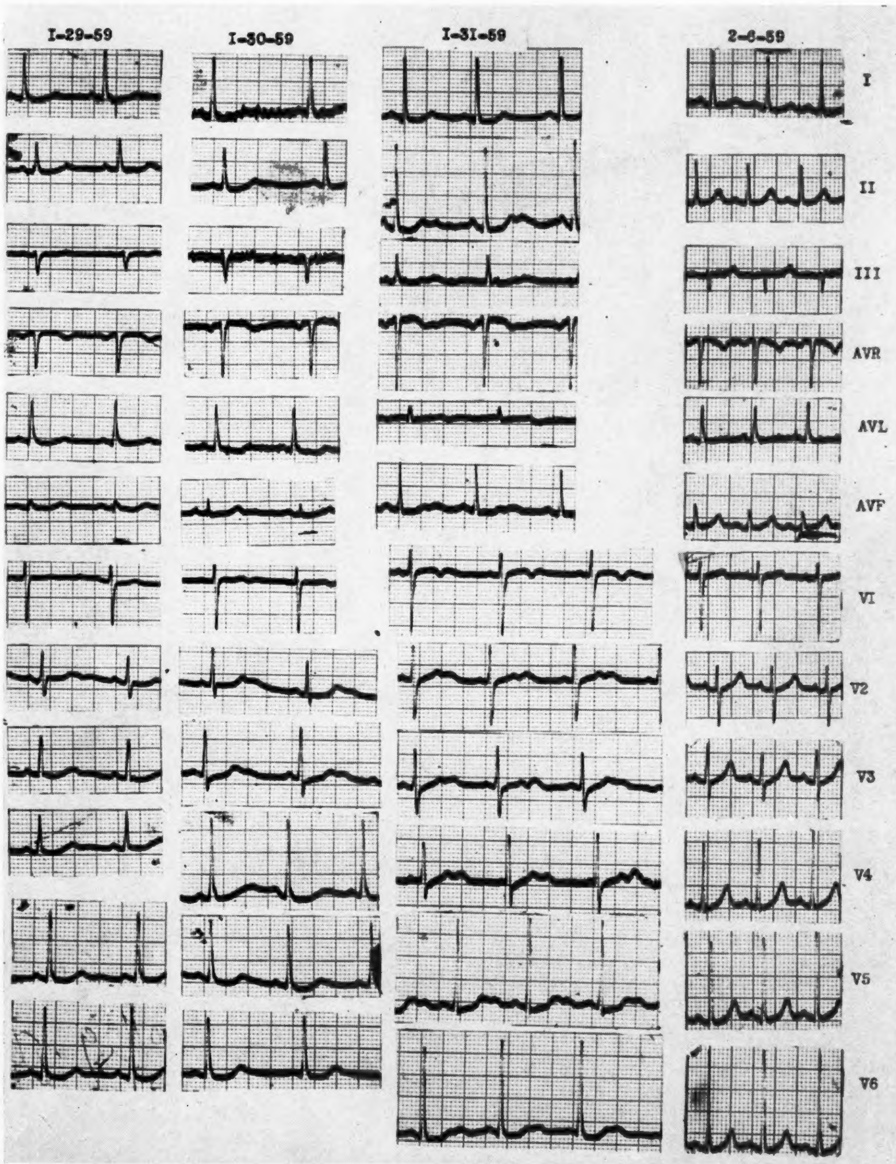

Fig. 3. Patient 6. The preoperative electrocardiogram and serum electrolytes (Jan. 29, 1959) were not remarkable. Three hours after ventriculography and craniotomy (Jan. 30) an electrocardiogram revealed prominence of the U waves and prolongation of the Q-T interval (39 per cent). Serum electrolytes were normal on this date. On the first postoperative day (Jan. 31) the prominence of the U wave was more striking. It merged with the descending limb of the T wave, giving it a broad appearance and a double peak. The tracing of Feb. 6 is normal except for sinus tachycardia due to associated fever. Postoperative serum electrolytes were normal.

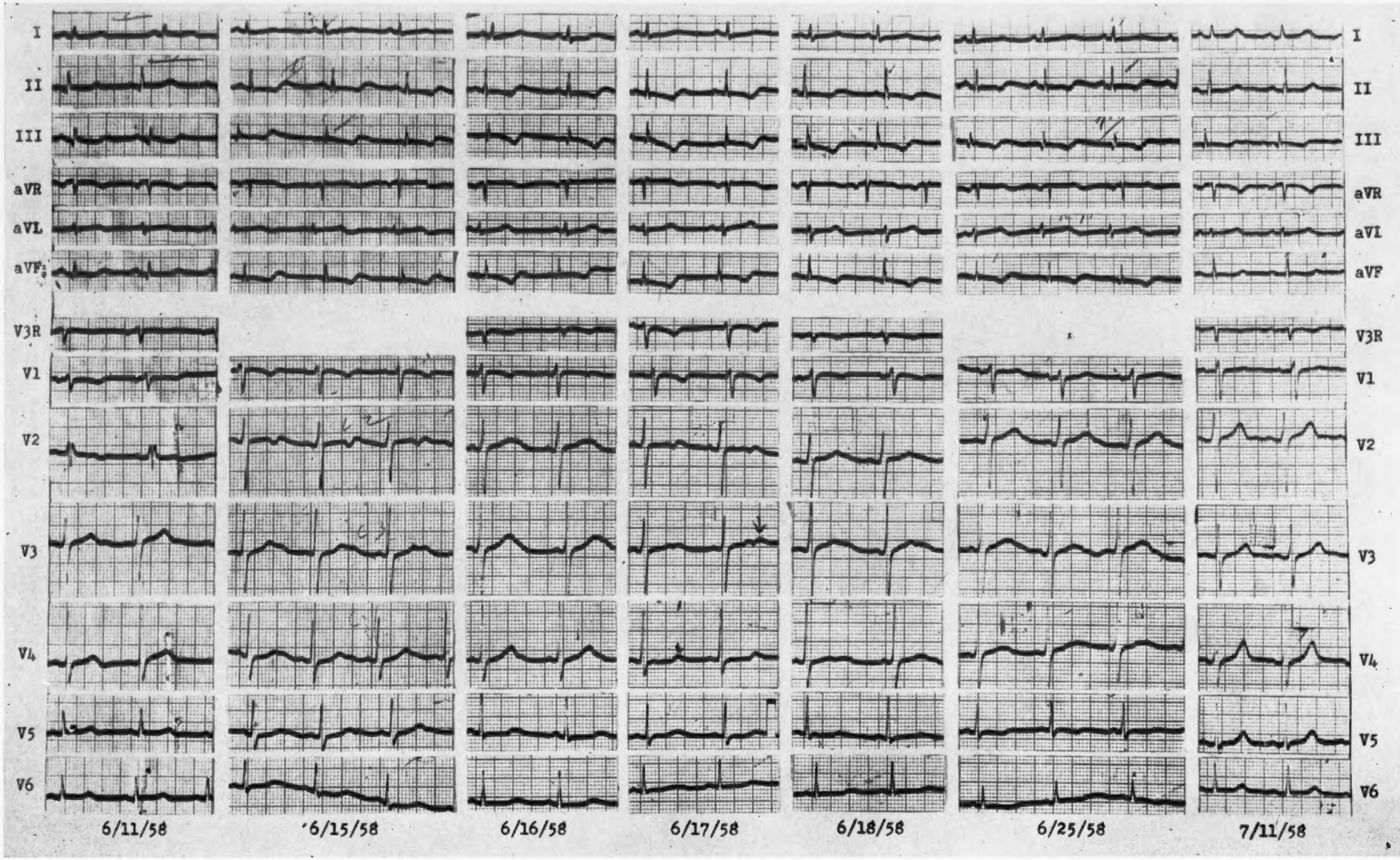

Fig. *4*. Patient 36. The preoperative tracing of June 11, 1958, is normal. The tracing of June 15 was taken 2 days after the pneumoencephalogram and demonstrates prominent U waves which merge with the descending limb of the T wave and Q-T prolongation (47 per cent). A diphasic T wave is present in Leads II, III, and aV_F of the minus-plus type. The following day (June 16) the T waves in Leads II, III, and aV_F are more deeply inverted, whereas the T waves in the right precordial leads are taller and merge more completely with the U waves. The Q-T interval remains prolonged. In the tracings of June 17 and June 18 the T waves in the right precordial leads are of diminished amplitude, the prominence of the U waves and Q-T prolongation persist. After the burr holes were made (June 24), the T waves became inverted in Leads V_5 and V_6. The tracing of July 11 has returned to normal, 4 weeks after the first operative procedure. Postoperative electrolytes were normal.

lead to myocardial damage, as demonstrated by the finding of infarcted areas, congestion, and hemorrhage at autopsy. These changes were more pronounced when the animal received eserine or acetylcholine, or when vagal stimulation was performed in the unanesthetized state. Some of these animals were protected from arrhythmias and myocardial effects by pretreatment with atropine.[21,22] Clinically, it has been shown that serious cardiac arrhythmias can be prevented by increasing the depth of anesthesia during operation on the arterial system at the base of the brain. This protection occurs, presumably, by blocking damaging neurogenic stimuli to the heart.[23] A state of excessive vagal stimulation has been implicated as the cause of electrocardiographic changes after pneumoencephalography and cranial trauma.[9,12]

This short review seems to leave little doubt concerning the profound myocardial effects of autonomic dysfunctions under a variety of circumstances.

It is our contention, then, that most of the changes observed in the electrocardiograms in this group of patients represent an alteration in myocardial function brought about by a temporary state of excessive stimulation of the vagus and sympathetic nerves. Whether this excessive flow of reflexes, created by irritation of various cerebral centers by the various neurosurgical procedures, leads to biochemical, anatomic, or combined changes in the myocardium has not been elucidated to date.

Summary

The electrocardiographic alterations are reported in 37 patients who underwent various neurosurgical procedures. Striking changes were observed, the chief of which consisted of alterations in the T wave, prolongation of the Q-T interval, and increase in the amplitude of the U wave. Various considerations are discussed in an attempt to elucidate the mechanism of these findings. No significant alteration was noted in the serum electrolytes during the postoperative period. It is difficult to conceive that the electrocardiographic changes represent primary myocardial changes, because the great majority of patients were without clinical evidence of cardiovascular disease and had an average age of 38.7 years. The electrocardiographic changes are most readily explained as being secondary to alterations in cerebral function after the various neurosurgical procedures.

We wish to thank Dr. Robert A. Groff, Professor and Chairman of the Department of Neurosurgery at the Graduate Hospital and Graduate School of Medicine of the University of Pennsylvania, for his cooperation and permission to investigate his patients during this study.

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Experimental and laboratory reports

Effects of selective myocardial stimulation or depression induced by intracoronary administration of drugs or by obstruction of major vessels. Studies with the dog ultralow-frequency ballistocardiogram

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The chief difficulties of animal experimentation with the ballistocardiograph (BCG) have been overcome with the ultralow-frequency technique,[1,2] so that additional experiments with this method give promise of advancing our knowledge in at least two directions. The first is that of special situations permitting a test of the method. As it has been used so far, the BCG records the forces which have their origin in the contraction of the heart. One hardly needs to be reminded that, although cardiac forces play a dominant role in the genesis of the force ballistocardiogram, the pressure in the vessels and their elasticity certainly affect the relation between cardiac forces and amplitude and form of the the record. We hoped to learn more about these noncardiac factors by studying the changes in the record caused by drugs which produce acute physiologic effects on the vessels alone, or on the heart alone. For this purpose we employed a new technique of selective intra-arterial injection which could restrict the action of the drug to one or the other of these vascular compartments.

Our second aim was of more general interest. The results of the action of drugs and other agents on cardiac contractility are usually described in the well-known terms of stimulation and depression, terms which, it must indeed be remembered, are extremely inexact. Knowledge of the force ballistocardiogram and of certain aspects of the pulse now permits a more precise understanding of important aspects of the performance of the heart than had hitherto been available. We were interested, therefore, in attempting a more exact description of the changes in cardiac performance which are found in a few of the common physiologic stresses that can readily be set up in acute experiments on animals.

Methods

This study was performed on an ultralow-frequency ballistocardiograph (UF-BCG) which was built especially for acute experiments with dogs. The instrument consisted of a rectangular frame (1.8 by 50 cm.) of hollow aluminum tubing (3.7 cm. in diameter) covered by lightweight canvas. This platform was suspended from the

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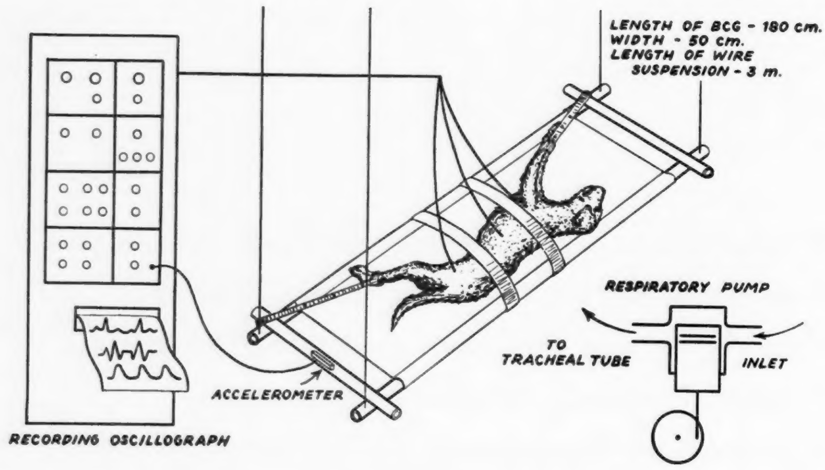

Fig. *1*. Ultralow-frequency dog ballistocardiograph (UF-BCG).

ceiling by means of 4 light steel cables which were about 3 meters in length. The natural frequency of the UF-BCG was 0.3 cycles per second. No external damping was used. Acceleration was transduced directly by means of a small (weight of 56 grams) variable capacitance accelerometer, which was built for us by Dr. Walter J. Gamble. The weight of the unloaded platform was 3.25 kilograms (approximately one tenth of the average weight of the dogs used in the experiment). The signal from the accelerometer was fed into a D.C. amplifier and recorded on a 4-channel Sanborn oscillograph, which allowed for concurrent monitoring of the ECG, systemic blood pressure, right or left atrial pressure, and respiration (Fig. 1).

Calibration of the instrument was obtained by the ratio, $D/(L \times d)$ = sensitivity (expressed in terms of gravities per centimeter), in which D is displacement of the bed (centimeter), L is length of suspension (centimeter), and d is displacement of the pen on the paper.

Systemic arterial blood pressure was measured intraluminally from the femoral artery by means of a Lilly variable capacitance manometer or a Statham pressure transducer connected to a rigid polyethylene catheter, the signal of which was fed into a D.C. amplifier coupled to a multichannel Sanborn recording oscillograph. The recording system was accurately calibrated against a mercury manometer each time before use for linearity and accuracy of response.

The dogs used throughout the experiments were specially selected large mongrels or boxers, 30 to 35 kilograms in weight, which were in optimal nutritional condition and had good muscle tone. They were anesthetized with morphine (3 mg. per kilogram, intramuscularly) and a combination of equal volumes of Dial and urethane in solution (100 and 400 mg. per milliliter, respectively); the dosage was 0.25 ml. per kilogram, intravenously. One or both femoral arteries were cannulated for the recording of blood pressure or for insertion of catheter balloons, and one femoral vein was exposed and cannulated for injection of the drug. A plastic cannula was inserted routinely into the trachea.

Each dog was placed on his right side, his limbs were secured to the frame of the BCG by means of conventional leather straps, and wide (6 cm.) canvas belts were tightened across the chest and abdomen in order to obtain maximum coupling of the body to the bed. Spontaneous respiration was stopped by means of decamethonium bromide (0.2 mg. per kilogram, intravenously) while an adequate respiratory exchange was maintained by means of an Ideal Starling pump connected to the tracheal cannula. The connections were such that no appreciable drag was exerted on the platform.

Insertion of modified catheter balloons into the pulmonary artery, aorta, and venae cavae (inferior and superior) was performed under fluoroscopic guidance. The position of the balloons was verified at

autopsy at the end of each experiment. A rigid metallic catheter of a type previously described[7] was introduced through the left carotid artery into the circumflex segment or the anterior descending branch of the left coronary artery for direct intracardiac injection of the drug. In two experiments, both branches of the left coronary artery were catheterized at the same time. All of these studies were conducted without opening the chest.

Results and discussion

Certain theoretical concepts should be presented prior to setting forth the results of our experiments. The views held by physicists for many years with regard to mechanical performance are applicable to the assessment of cardiac function. When a force sets a body in motion, as the energy supplied by the heart sets the blood in motion, an exact description of the effect produced requires three separate headings: (1) effects related to displacement of blood, or cardiac output; (2) effects related to the velocity imparted to the blood, including work in the Newtonian sense and friction; (3) effects related to the acceleration of blood, or cardiac force.

Relationships have been demonstrated between these three aspects of cardiac performance and certain aspects of ordinary physiologic measurements. Thus, the BCG, as we use it, is a force recorder, and both the depth of the I wave and the slope of the H-I segment have proved to be quantitatively related to the force manifested by the accelerating blood at the onset of contraction.[3] The slope of the advancing front of the pulse wave has also proved to be correlated with the acceleration of the ejected blood and, conversely, with cardiac force[3]; the amplitude of this wave, the pulse pressure, with Newtonian work[4]; the area under the systolic portion of the pulse wave (consideration is given to the blood pressure or the elasticity of the vessels), with cardiac output.[3-5]

The regression equations used to derive a quantitative estimate of each of these three aspects of cardiac function were derived from experiments on human cadavers, but they could not be applied to dogs without additional study. Therefore, no quantitative evaluations have been attempted in our studies with dogs. Nevertheless, we find it of great interest to trace the direction of the changes that occurred in these three aspects of cardiac function during the stimulation and depression of left ventricular contractility produced in our acute experiments with dogs. There is no reason to expect that these three aspects will always vary together, and we were interested in observing whether the stresses of our experiments affected one variable more than another.

Early in the experiments our attention

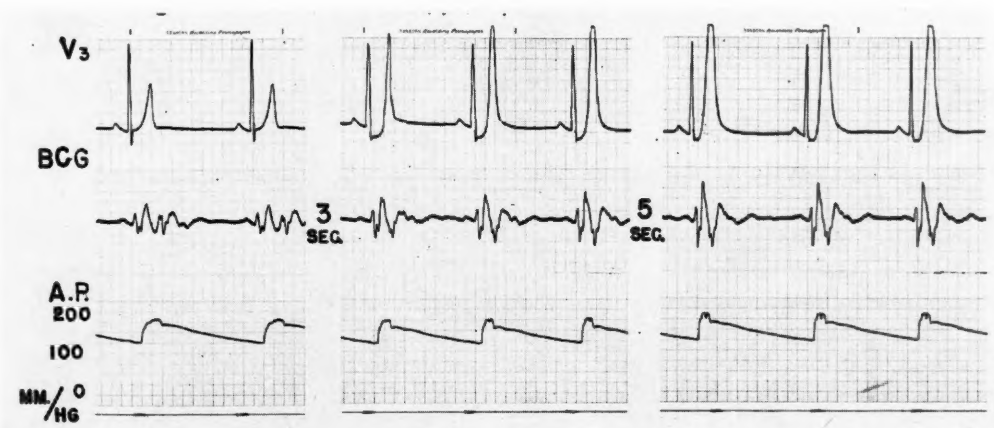

Fig. 2. Response after the injection of a sympathomimetic amine (epinephrine, total dose of 5 μg) into the anterior descending branch of the left coronary artery. Note the increase in amplitude of the I-J wave and the change in its slope. Systolic blood pressure is practically unchanged except for the steeper slope of the pulse wave. In all figures, the paper speed was 50 mm. per second. The control record is always the first section on the left. The markings at the bottom of each of the figures are in seconds.

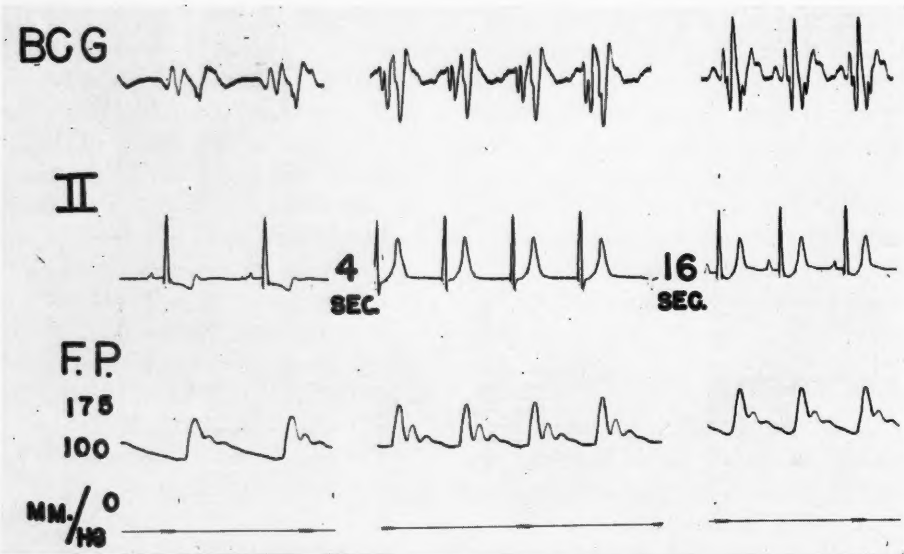

Fig. 3. Response after the injection of epinephrine (total dose of 5 μg) into the circumflex branch of the left coronary artery. Note the onset of nodal rhythm. The amplitude of the ballistocardiogram is increased, but this improvement is not so conspicuous as that after the injection into the anterior descending branch (Fig. 1). A marked improvement appears after 16 seconds, when the sinoatrial node again prevails as pacemaker.

was attracted to changes in the J wave which seemed to be of peripheral rather than of cardiac origin. The J wave, according to Noordergraaf's quantitative theory of the ballistocardiogram,[6] is chiefly the result of a footward acceleration of blood in the descending aorta and in the arteries of the legs. A much smaller factor is the deceleration of blood leaving the heart as it loses its headward velocity when reversing its direction of flow in the aortic arch and in the bifurcation of the pulmonary artery. Thus, the form and amplitude of the J wave depend on more than one factor. Of these, the most important factor is the acceleration with which the stroke volume is ejected by the heart. Other factors are the elasticity of the vessel walls and the blood pressure—the latter, because vascular elasticity changes as intravascular pressure changes.

Cardiac stimulation. By injecting sympathomimetic amines (epinephrine, norepinephrine, and isoproterenol) which have powerful cardiac inotropic and chronotropic effects into the circumflex or anterior descending branch of the coronary artery, we tried to assess the effects of changes in left ventricular contractility accompanied by little or no peripheral change. It is thus possible to achieve a high concentration of the drug in selected areas of the cardiac musculature and to elicit local responses which are not obscured by systemic vascular reactions. Although it cannot be denied that reflex effects on the vessels might follow the changes induced in the muscle of the left ventricle, we believe that this technique is the nearest approach to a "pure" cardiac stimulatory situation that has been achieved in an intact animal, and that the results are of interest for this reason.

In the majority of dogs the circumflex branch of the left coronary artery supplies blood to the atrioventricular node as well as to the septum and the posterior part of the left ventricle, whereas the anterior descending branch distributes blood to the anterior part of the left ventricular mass. The injection of a small dose of a sympathomimetic amine into the anterior descending branch of the left coronary artery is, therefore, followed by an immediate and marked increase in amplitude of the systolic complexes. As little as a total dose of 5 μg of epinephrine brings about a 100 per cent increase in the amplitude of the I-J wave, and its slope becomes very steep. Since the drug does not reach the conduction tissues of the heart, there is no chronotropic response; the ballistic effect is due

primarily to increased contractility of the muscle of the left ventricle, with increased acceleration of the blood from the ventricle and a more complete and rapid ejection (Fig. 2).

On the other hand, the injection of a sympathomimetic amine into the circumflex branch of the left coronary artery, because of its different distribution, is attended by an altogether different response. This is characterized by direct stimulation of the conduction tissue (positive bathmotropic and chronotropic effects) which leads to the transitory onset of a nodal rhythm (rythme nodal moyen) which consists of a succession of normal QRS-T complexes not preceded by a P wave.[7] The atrioventricular node, directly stimulated by the drug, forms impulses at a faster rate than does the sinoatrial node, and thus acts as a temporary pacemaker.

Dissociation by interference is another interesting effect which often follows the intracoronary injection of sympathomimetic amines. Under such circumstances, one sees complete independence of the electrical and mechanical activity of the auricles and ventricles. The atrioventricular node forms impulses at a higher frequency than does the sinoatrial node; however, a retrograde block prevents the atrioventricular impulses from reaching the auricles and perturbing the sinoatrial node, which is discharging at a slower rate. This phenomenon, described by Wenckebach and Winterberger[8] in 1927, is well known in the clinic, especially in patients who have received digitalis or atropine.

Fig. 3 shows the effects which followed the injection of epinephrine (total dose of 5 μg) into the circumflex branch of the left coronary artery. The ECG shows that there was an immediate shift in the pacemaker with the induction of a nodal rhythm, and a marked increase in heart rate. The form of the ballistic record was profoundly changed. There was a conspicuous increase in amplitude of all waves except H, which became smaller, and a deep notch appeared on the H-I segment; the area under the systolic pulse wave was almost unchanged and the blood pressure rose only a little, but there was an increased steepness of slope in the ascending limb of the peripheral pulse wave. As soon as normal atrioventricular conduction was reestablished with re-emergence of the sinoatrial node as the pacemaker, the form of the ballistic record returned to normal, with an increased amplitude of all its systolic components. This improvement is probably due to improved filling consequent to re-establishment of normal atrioventricular dynamics. This is the type of response which usually attends the injection at this site of epinephrine, norepinephrine, or isoproterenol, three sympathomimetic amines which possess to the highest degree the capacity for stimulating

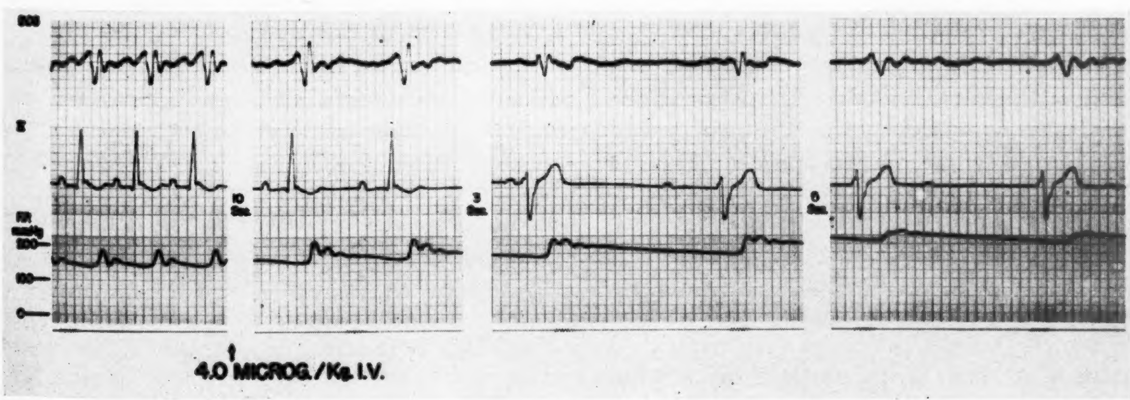

Fig. *4*. Response after the injection of a sympathomimetic amine having no inotropic or chronotropic action (methoxamine, 4 μg per kilogram). After 10 seconds systemic blood pressure rises gradually, whereas the heart rate slows. A few seconds later systolic pressure is very high (above 200 mm. Hg) and there is marked bradycardia due to baroceptor activation. The ballistic tracing decreases in amplitude. The rise in pressure induces irregularities of intracardiac conduction. Note the almost complete disappearance of the J wave in the third section of the tracing.

the chronotropic and inotropic properties of the heart.

From these results we conclude that the chief effect of the stimulation was on the cardiac force, for the ballistocardiogram increased greatly in amplitude, and the slopes of the I and the H-I waves increased as it did so. The slope of the pulse wave front was also steeper, whereas the changes in the pulse pressure and in the area under the pulse wave were far less evident. This suggests that, in our experiments, sympathomimetic amines administered by this method resulted in an increase in myocardial contractility rather than an increase in stroke volume.

This interpretation of the ballistic changes was further substantiated by the intracoronary administration of sympathomimetic amines in open-chest dogs in which a Walton strain gauge had been directly attached to the left ventricular muscle. The increase in amplitude of the systolic complex of the ballistocardiogram appeared in all cases to be directly correlated with the improvement of myocardial contractility consequent to the administration of those sympathomimetic amines which have a direct stimulatory effect on the release of energy by the ventricular muscle.

Peripheral vasoconstriction. In these experiments we sought to avoid the combination of peripheral and cardiac effects which are produced by most sympathomimetic amines when administered intravenously. We chose methoxamine (Vasoxyl), a sympathomimetic amine devoid of any positive cardiac inotropic or chronotropic actions, and injected it intravenously in doses of 4 mg. per kilogram, three times in each of 15 animals. Whenever the drug was administered after atropine had been injected or cold had been used to block the vagus nerves, the type of response obtained was unaltered except for a less pronounced bradycardia.

Fig. 4 shows the results of a typical experiment. Ten seconds after the administration of the drug the heart rate slowed and the ballistocardiogram increased in amplitude. The pulse wave rose more steeply and the pulse pressure increased, although the rise in systolic and diastolic pressure was as yet small. This period of stimulation was transient; 3 seconds later, evidence of heart block appeared in the ECG, and the heart rate became much slower. At this time, the ballistocardiogram decreased in amplitude, the H-I slope was less steep, and the J-wave amplitude was reduced. The pulse pressure was somewhat diminished, and the fall in blood pressure during diastole was extremely slow. Five seconds later these effects appeared to be exaggerated still more. The blood pressure was higher and the ballistocardiogram became distorted, with the J wave scarcely rising above the base line.

We interpreted these findings to mean that, confronted with increasing peripheral resistance, the heart rate became slower after an initial period of stimulation because of improved filling. The cardiac force, the work, and the output per beat were all increased during this brief period, although, judged on a per-minute basis, this increase was not large. A few seconds later the high peripheral resistance after heart block had developed, indicated not only by the high blood pressure but also by the very slow fall of blood pressure during diastole, proved to be too much for the heart, and all aspects of its function were severely depressed.

These cardiac effects cannot be attributed to the direct action of methoxamine on the heart; rather, they must be thought of as consequences of the greatly increased resistance to ejection or as secondary effects due to activation of carotid and aortic baroceptors by the rise of blood pressure, or as both. In this experiment an interesting distortion of the form of the ballistocardiogram developed: the J wave was greatly reduced and almost obliterated while the preceding I wave was only slightly reduced in amplitude. We suggest the following explanation: The I wave is to be attributed to the footward recoil of the body when blood is accelerated headward early in the ejection; the chief factor in the genesis of the J wave is the recoil of the body to the footward acceleration of the long column of blood in the large thoracic and abdominal aorta and the arteries of the legs. The abnormality of form that is seen at the height of the action of methoxamine, i.e., disproportionate reduction of the J wave, is what one would

expect if the mass of ejected blood, after entering the aorta and pulmonary artery with little less than its usual acceleration, were gradually damped and, instead of immediately driving the long column of blood before it, were accommodated in the aorta for a brief period by unusual stretching of the aortic wall. Under such circumstances the long column of blood in the thoracic and abdominal aorta would be accelerated much more slowly than is normal, and the forces which produce the J wave would be greatly reduced. The extraordinarily slow fall of femoral pressure during the long diastole indicates that peripheral resistance was greatly increased during the absence of the J wave. Such abnormal resistance would certainly oppose and reduce the acceleration of the aortic and femoral blood. This line of thought was further tested in the following experiments.

Increased resistance from obstruction of the thoracic aorta. Fig. 5 shows the typical effect of the sudden inflation of a balloon mounted on the tip of a catheter in the thoracic aorta, an experiment which was performed three times consecutively in 5 dogs. The high aortic obstruction, the completeness of which was indicated by immediate fall to zero of the femoral blood pressure, was accompanied by a marked distortion of the J wave, which was deeply split, greatly reduced in amplitude, and broadened. Some reduction in the depth of the I wave and of the H-I slope accompanied this change. The form of the ballistocardiogram returned to normal as soon as the obstruction was removed.

One must remember that a balloon inflated within a vessel effectively stops the flow of blood but it does not stop the transmission of forces. Both ends of the air-filled balloon are in contact with the blood in the aorta. The rise in systolic blood pressure above the balloon dents its upper surface and increases the pressure inside the balloon. This increased pressure distends the lower surface of the balloon, thus imparting a force to the column of blood below. The inflated balloon stops the flow of blood, but the force passes through it, although distorted by the physical properties of the air-filled balloon which vary with its pressure. One notes that the pulse is plainly visible in the tracing of the femoral pressure during the period of obstruction, although the pressure below the balloon is so low that a considerable change in volume would be necessary to produce the small change in the recorded pressure.

The notching in the J wave may well be a result of dissociation of the forces from the two sides of the heart; those from the left side are delayed in time because the

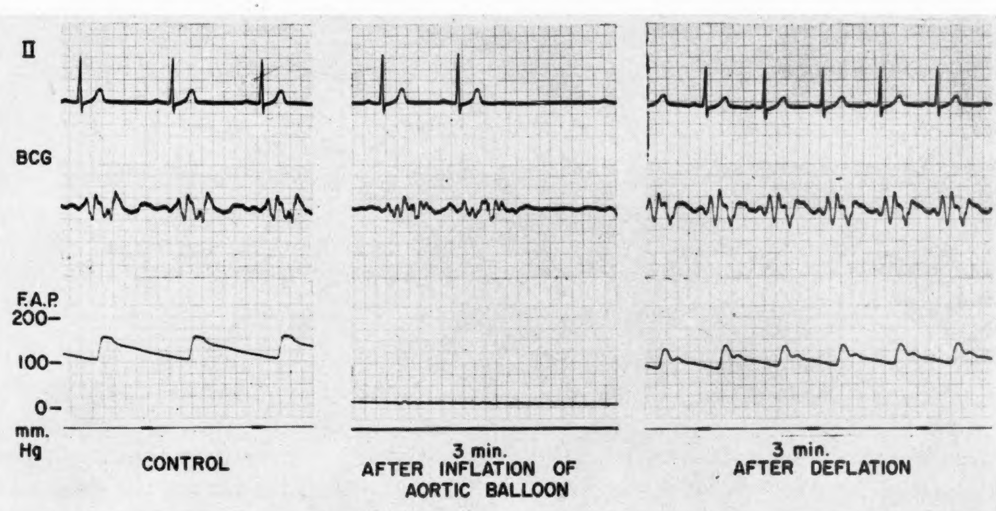

Fig. 5. Typical effect of rapid obstruction of the thoracic aorta by means of the sudden inflation of a balloon mounted on the tip of a catheter. Note the reduction in amplitude of the ballistocardiogram and the disappearance of the femoral pulse. The ballistocardiogram returns to normal immediately after deflation of the balloon. Three minutes later there is an increase in amplitude over the control tracing.

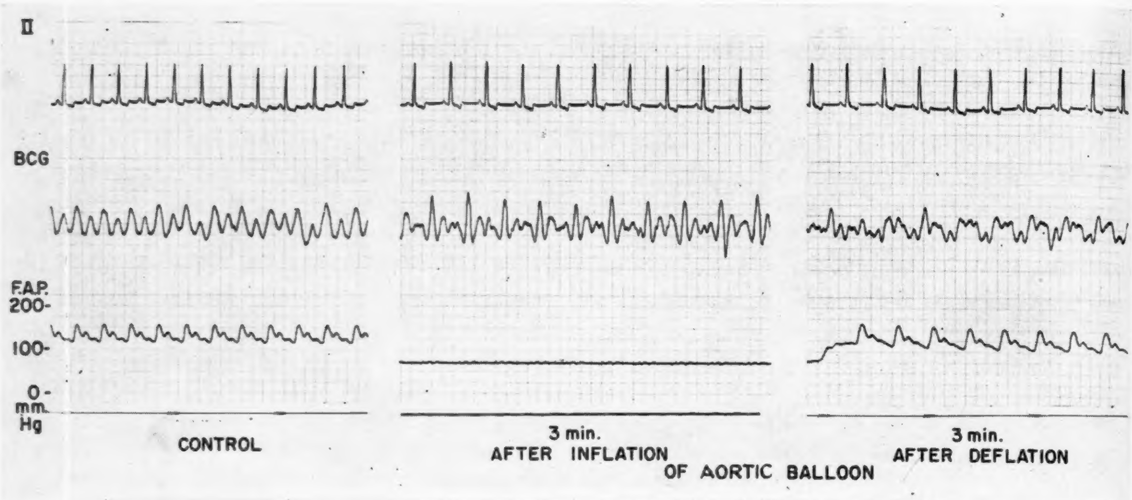

Fig. *6*. Effect of gradual obstruction of the thoracic aorta by means of the slow inflation of a balloon mounted on the tip of a catheter. Femoral pulse pressure is reduced to a ripple. Improvement of the ballistocardiogram during inflation is probably the result of slowing of the heart rate. Upon deflation of the balloon, the ballistic tracing becomes distorted.

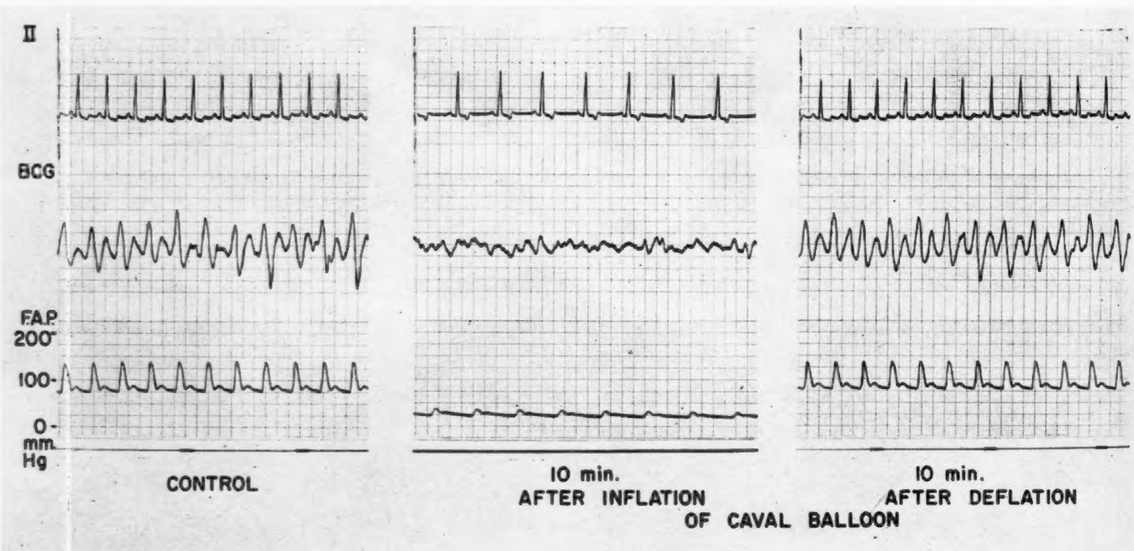

Fig. 7. Effect of complete obstruction of the inferior vena cava by means of inflation of a catheter balloon. Note the almost complete disappearance of all systolic complexes of the ballistocardiogram. Femoral blood pressure is drastically reduced and pulse pressure is very small. Release of obstruction of the vena cava induces complete reversal of the effect.

high resistance in the aorta has delayed ejection from the left ventricle. There is no corresponding increase in resistance to right ventricular ejection. Indeed, the splitting of the J wave has been produced repeatedly in experiments on cadavers when systole has been simulated by asynchronous injection of the pulmonary artery before the aorta.[9]

The broadening and slow descent of the J wave to the base line, like the similar change described in aortic stenosis in man, can be attributed to the diminished acceleration and deceleration of blood below the obstruction, since it is the deceleration of blood units in the long aortic column which normally brings the J wave back to the base line at the usual time, and which may continue to form the K wave.

When we used a slight difference in technique, we secured such a different result in another dog that we believe it should

be discussed (Fig. 6). In this case, a balloon was gradually inflated in the thoracic aorta. The physiologic state of the heart was very different in this experiment: in the experiment illustrated in Fig. 5, the heart rate was 70 beats per minute; in this experiment, 240 beats per minute. Such a rapid rate causes difficulty in interpreting the ballistocardiogram, which should be explained here. Inspection of the ballistocardiogram of the heart of a dog in good condition, such as the ballistocardiogram reproduced in Fig. 4, shows that the terminal complex, the L, M, and N waves, often relatively larger in dogs than in man, occurs about 0.3 second after the peak of the R wave. Obviously, therefore, when the cardiac cycle is as short as in the experiment illustrated, the last waves of one complex are superimposed on the first waves of the following complex, and distortion occurs. This is the case in the control tracing in this experiment, and exact interpretation of the record was difficult.

Nevertheless, interesting changes followed the slow inflation of the balloon in the thoracic aorta. The heart rate slowed considerably (to about 180 beats per minute) and there was notable improvement in the ballistocardiogram, which returned to normal. After deflation of the balloon, despite the normal blood pressure and pulse wave contour, the ballistocardiogram became more abnormal than it had been before.

This unexpected result may be compared to certain equally unexpected results in the clinic when a stress, such as exercise, has occasionally converted an abnormal ballistocardiogram into a normal one. The interpretation of these phenomena has been as follows: Cardiac stimulant drugs often convert an abnormal to a normal ballistocardiogram, and this causes no surprise. Exercise or any other type of stress which stimulates the heart by hormonal or nervous influences may produce a similar stimulating effect. In our case the aortic obstruction proved to be a challenging stimulus to which the heart responded with an increased contractility and an improved performance.

The rapid deterioration of cardiac function after the removal of the aortic obstruction is equally interesting and is consistent with the same concept. The extreme abnormality which then developed suggests an incoordination of cardiac forces. Since the pulse wave is not very different from that of the control period, the disorganization of the ballistocardiogram can

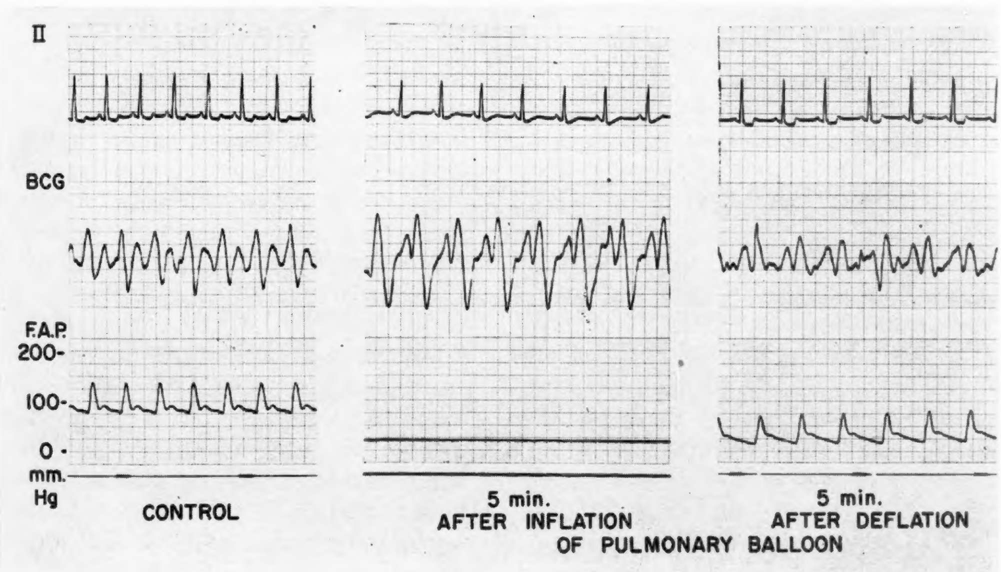

Fig. 8. Typical result of obstruction of the main trunk of the pulmonary artery by means of a catheter balloon. The great increase in amplitude of the systolic complexes of the ballistocardiogram is an unexpected result. Acute tricuspid insufficiency, which allows backflow of blood into the venae cavae, may account for this response.

best be explained as asynchronous generation of forces from the two sides of the heart. This type of unpredictable response to various stresses is encountered quite often both in normal and pathologic conditions.

Hypotension produced by caval obstruction. A balloon was inflated in the inferior vena cava ten times in 4 dogs. Fig. 7 is an example of the result secured in this experiment. The systolic ballistic waves are easily seen in the control tracing despite the fast heart rate which caused the N wave to be superimposed on the H wave of the following beat.

The effect of obstruction of the vena cava was profound. The ballistocardiogram was greatly reduced in amplitude and so distorted that the waves could not be identified with confidence in many complexes. The H-I slope was almost flat in some complexes and greatly flattened in all; similarly, the pulse wave front had a very gradual rise. The pulse pressure fell to less than one fifth of its control value. The area under the systolic pulse wave was reduced to a small fraction of its former value.

Obviously, the cardiac forces, work, and the stroke volume were greatly reduced. The lack of filling greatly handicapped the heart, and all aspects of its performance were depressed. The J wave was not increased, as after administration of vasodilating drugs, because, despite the reduced peripheral resistance, the stroke volume was so small and ejection was so slow that the column of blood in the thoracic and abdominal aorta was accelerated very feebly.

Cossio and co-workers[10] claimed that the impeded filling of the heart in open-chest dogs caused an increased amplitude of the ballistocardiogram, a view which was supported for a time by Thomas and co-workers.[11] On the basis of these results the theory that the ballistocardiogram had its origin chiefly in the movement of blood was challenged. Our results are similar to those of Honig and Tenney[2] and to those of Scarborough,[1] and so support the classic viewpoint. We have no intention of reviving the controversy here. It would seem, however, that experiments performed with improved techniques have not confirmed the results of Cossio and of Thomas and their associates.

Obstruction of the pulmonary artery. The inflation of a balloon in the pulmonary artery produced an effect which was totally unexpected. Fig. 8 shows a typical result. Similar results were secured four times in 2 dogs. Again, the interpretation of the control ballistocardiogram was made difficult by the rapid heart rate, but the distortion appeared to be slight. The great increase in amplitude of the ballistocardiogram after obstruction of the pulmonary artery was striking. This increase was due chiefly to greater depth of the K wave, but the slope of the H-I segment was also clearly increased during the pulmonary obstruction, even though the femoral blood pressure had fallen almost to zero and no pulse beat was visible.

For some time we were at a loss to explain this most unexpected result and, indeed, considered the explanation suggested by Cossio and associates,[10] that movement of the heart itself might cause a ballistocardiogram even if no blood were ejected from the ventricle. One could not deny that under certain extreme circumstances this might be the case. Our results, however, are also in accord with another viewpoint which, consistent with other knowledge acquired recently, provides a more satisfactory explanation.

From McMichael and Shillingford's laboratory[12] have come a series of clinical observations which indicate that regurgitation through the tricuspid valve occurs frequently in clinical conditions; these investigators regard it as a compensatory mechanism which protects the right side of the heart against overdistention.

Also, in experiments with the frog, an animal with a single ventricle, Klensch[13] found that experimental obstruction of the aorta leads to a ballistocardiogram of increased amplitude. Analyzing this unexpected result, which was so similar to ours, he observed that great distention of the heart had rendered the tricuspid valve incompetent, and that the heart was vigorously pumping blood back into the great veins at every systole. Thus, the unexpected increase in the size of the ballistocardiogram could be attributed to this abnormal movement of blood.

Although the heart could not be observed in our closed-chest experiments, it is well known that the right side of the heart dilates rapidly when confronted by a resistance too great for its strength, and it seems inevitable that this happened in our experiments when the pulmonary artery was completely obstructed. The best explanation for our finding seems to be similar to that given by Klensch: the dilated heart, because of the relative insufficiency of the tricuspid valve, was vigorously taking blood from the veins and also pumping it back into them.

However, our attempts to obtain additional evidence without opening the chest were not altogether successful. Inflating a balloon in the inferior vena cava before inflating one in the pulmonary artery did not prevent the increase in ballistic amplitude; the inability of an inflated balloon to stop the forces has already been discussed in this paper. Also, measurements of pressure gave little information because in a low-pressure system, such as the veins, the relation of flow to pressure is far more remote than in the arteries.

Summary

By means of the ultralow-frequency technique, excellent ballistocardiograms were secured in experiments with anesthetized dogs. These records, together with those for femoral blood pressure, were employed to detect changes in cardiac function under various experimental conditions.

To secure cardiac stimulation in as pure a form as possible, drugs which stimulate cardiac action, in doses too small to give generalized effects but large enough to produce localized responses, were injected into both branches of the left coronary artery. To secure peripheral constriction in as pure a form as possible, drugs without direct cardiac action were injected intravenously.

From the changes in contour of the ballistocardiogram and of the blood pressure curves, the direction of the changes in cardiac force, work, and output was assessed. Cardiac stimulation usually increases all of these aspects of cardiac performance; depression usually decreases all of them. Some aspects were often affected more than others.

By means of balloons mounted on the tips of catheters, the effects of obstruction of the aorta, of the inferior vena cava, and of the pulmonary artery were observed. The latter gave a surprising result—a large increase in the size of the ballistocardiogram, apparently a result of tricuspid regurgitation.

By means of changes in peripheral resistance, marked changes in the J wave of the ballistocardiogram were produced. It seems evident that the amplitude of this wave can be altered by noncardiac as well as by cardiac factors. The causes of other abnormalities of ballistic form produced experimentally in the dogs are discussed.

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A scanner-computer for determining the volumes of cardiac chambers from cinefluorographic films

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Use of biplane cineroentgenographic and serial x-ray techniques for measurement of the volume of various cardiac chambers has been shown to be reasonably reliable.[1-3] The chief objection in practice is the tediousness of the various tracing operations and of the laborious calculations that are involved in some of the methods. In order to overcome this objection, consideration was given to the development of mechanical and electronic adjuncts to facilitate tracing chamber boundaries and to carry out the necessary calculations.

The method for which the instruments to be described were developed has been published in detail.[1] In the case of the left ventricle, it requires the tracing of two simultaneously filmed images (35-mm. film) recorded at a rate of 30 per second. Measurements of corresponding diameters of the two images are then made at 1-mm intervals from top to bottom, and the values are inserted into the usual equation for the area of an ellipse (or circle):

$$A = \pi \frac{d_1}{2} \cdot \frac{d_2}{2},$$

where d_1 is diameter obtained from one ventricular image, and d_2 is the corresponding diameter from the other, simultaneously recorded, image. Since diameters are measured at 1-mm. intervals, the area in square millimeters is numerically identical with the volume of a section of the ventricular cavity that is 1 mm. thick (Fig. 1). Total ventricular volume is merely the sum of all the sectional volumes.

In practice, it is necessary to trace up to 80 pairs of images for each run (4 to 8 cardiac cycles). Usually, from 50 to 70 diameters are measured on each pair of images, necessitating a vast number of separate multiplication and summing oper-

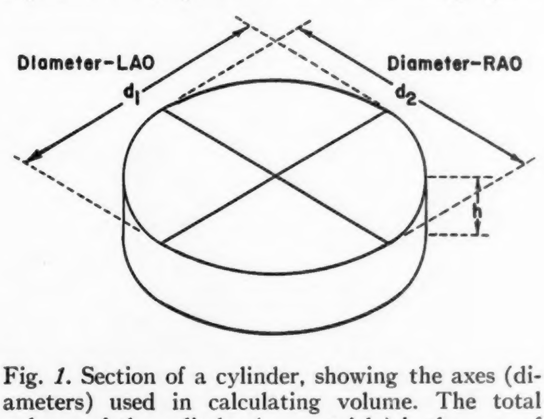

Fig. *1.* Section of a cylinder, showing the axes (diameters) used in calculating volume. The total volume of the cylinder (or ventricle) is the sum of those of the individual sections.

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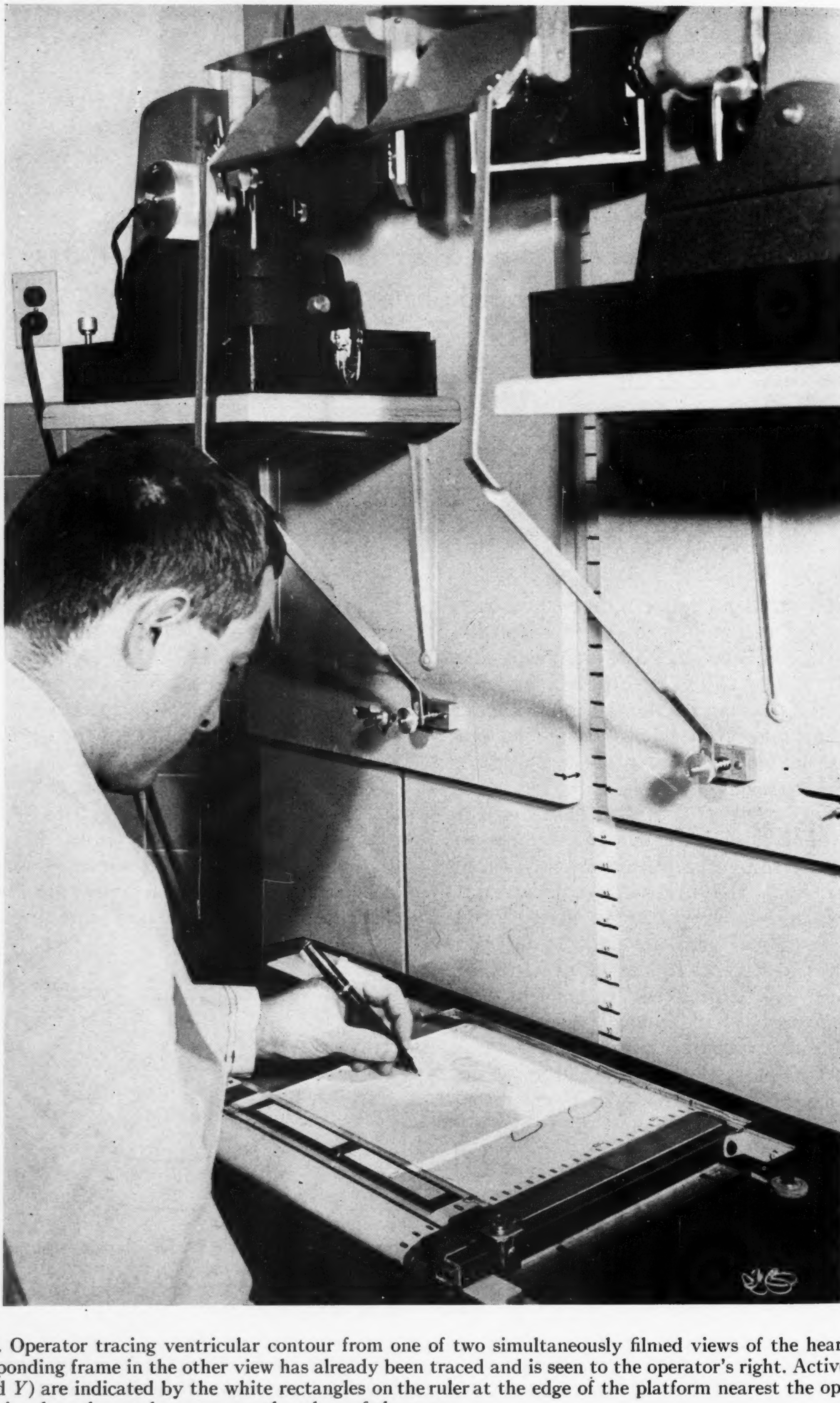

Fig. 2. Operator tracing ventricular contour from one of two simultaneously filmed views of the heart. The corresponding frame in the other view has already been traced and is seen to the operator's right. Active areas (X and Y) are indicated by the white rectangles on the ruler at the edge of the platform nearest the operator. Operational marks can be seen near the edges of the paper.

ations. It is not unusual for the calculations for a single run to occupy 3 workers for 2 to 3 weeks.

It was originally hoped that the entire measurement and calculation procedure could be done electronically. It was not feasible, however, to entrust tracing of chamber boundaries to an electronic scanner or densitometric device. This operation, for many reasons, requires judgment and constant comparison of sequential images. For this reason, tracing is done from 35-mm. original films, using a 16-mm. reduction print of the same original to establish the location of valve planes and other details. The process, with experience and the help of mechanical aids, goes rapidly.

Tracing equipment

Two 35-mm. still projectors are mounted on an upright standard as shown in Fig. 2. Images of individual frames are projected by use of appropriately placed front-surfaced mirrors onto a tracing platform in such a way that chamber images are relatively undistorted.[1] The tracing platform is designed to receive slotted roller paper, 27 cm. wide, on which corresponding chamber images can be very precisely located and traced (Fig. 2). Owing to the design of the scanner (see below), images must be traced firmly and definitely in black ink. Small operational marks are appropriately placed in order to instruct the scanner to commence or to cease measurement (Figs. 2 and 3). In the event that images do not fit easily into X or Y areas (Fig. 3), they can be reduced one half, and the final calculation corrected accordingly in the computer. Conversely, if images are too small to be handled accurately, their size can be doubled and the fact taken into account in final calculations.

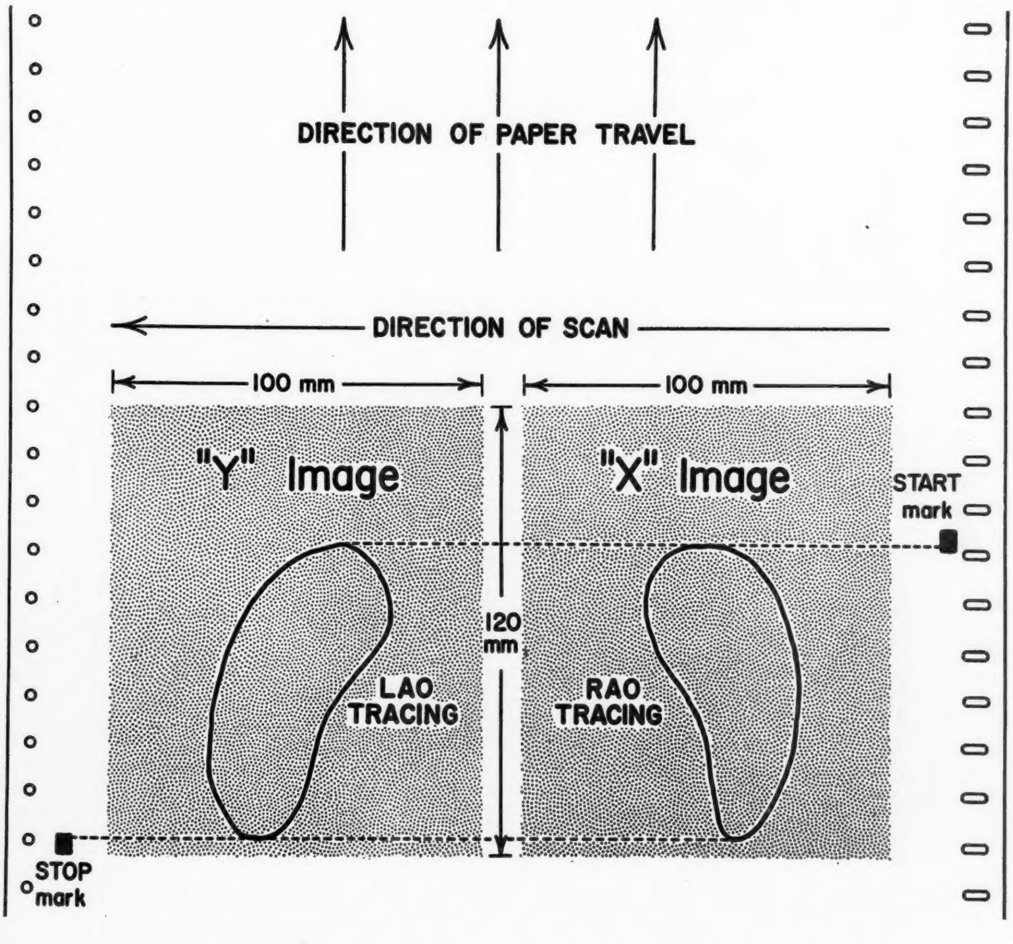

Fig. 3. Section of slotted paper bearing 2 ventricular tracings. Locations of operational (*start* and *stop*) marks, and the active areas (X and Y) are clearly shown.

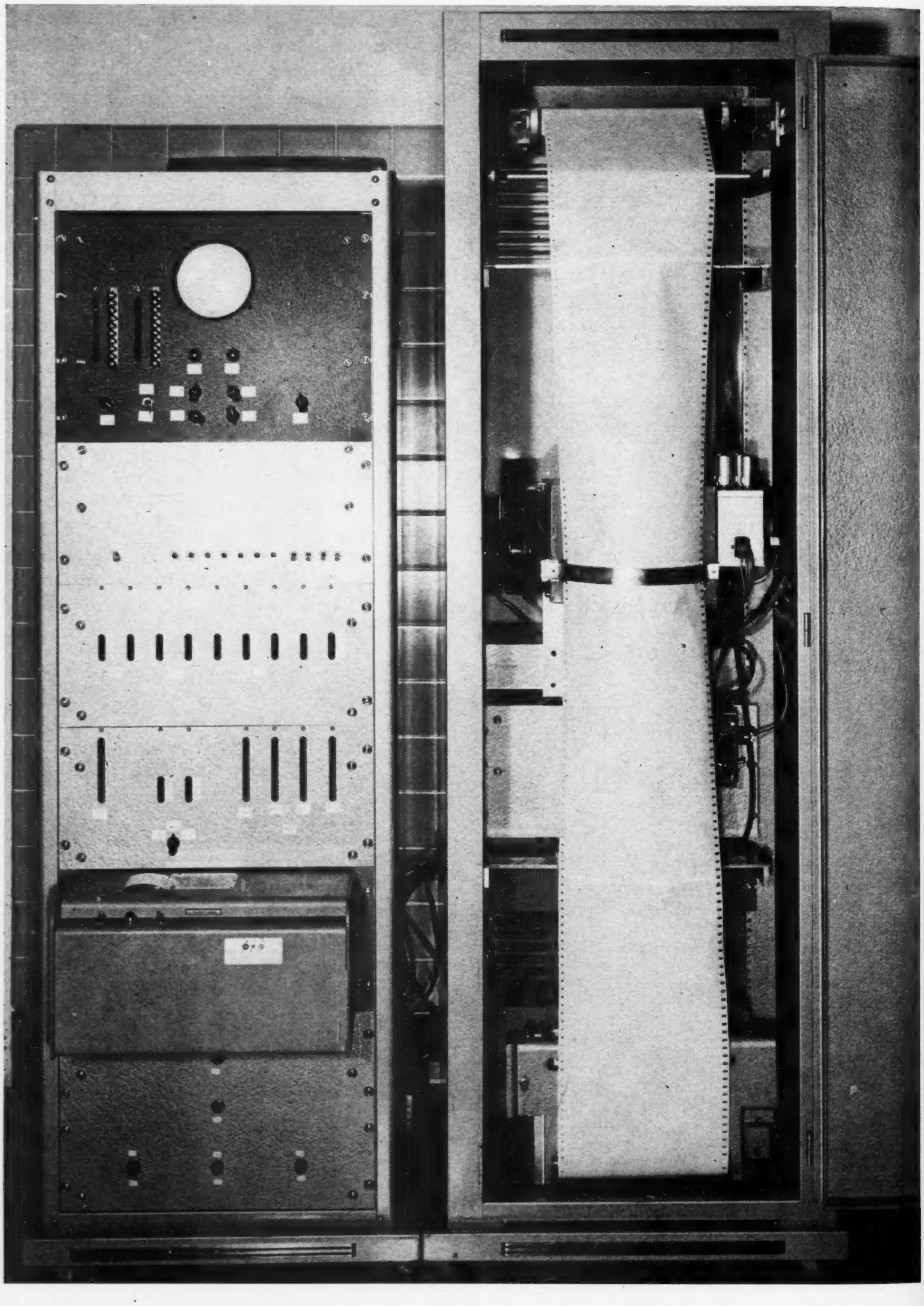

Fig. *4*. Over-all view of scanner (*right*) and computer (*left*). A roll of paper is flowing past the scanning slot from top to bottom. The oscilloscope is at the left (above) and the printer below.

Use of the tracing device permits the tracing of 50 to 100 pairs of images in 2 to 3 hours.

The scanner

In essence, the function of the scanner is to measure the diameters of the traced figures (Fig. 3) and to transmit the result to a photomultiplier tube which then transmits it to the computer.

The instrument consists of a light source and a series of mirrors which transmit a light beam onto the slotted paper flowing past the scanning aperture (Figs. 4 and 5). Beams reflected from the paper surface are led back to the photomultiplier tube and are interrupted only when a black mark on the paper is encountered. With appropriate placement of operational marks (Fig. 3), the counting mechanism of the scanner unit can be activated or deactivated so that only distances between the boundaries of a particular image (in X area or Y area, Fig. 3) are transmitted to the computer. The counting mechanism consists of a slotted disk, 25.4 cm. in diameter, on which is mounted a lens and scanning mirror (Figs. 5 and 6). The disk revolves at precisely 1,800 r.p.m. The various slots, numbered *1* to *5* in Fig. 6, are concerned with operational instructions and with actual measurement of distances within X and Y areas. For example, slot *1* (and the photoelectric diode to which it relates) is concerned with the mechanism of clearing the computer for its next calculation, and the operation that it controls is activated by the *start* mark (Fig. 3). Slots *2* and *3* are part of the mechanism for instructing the scanner to measure a di-

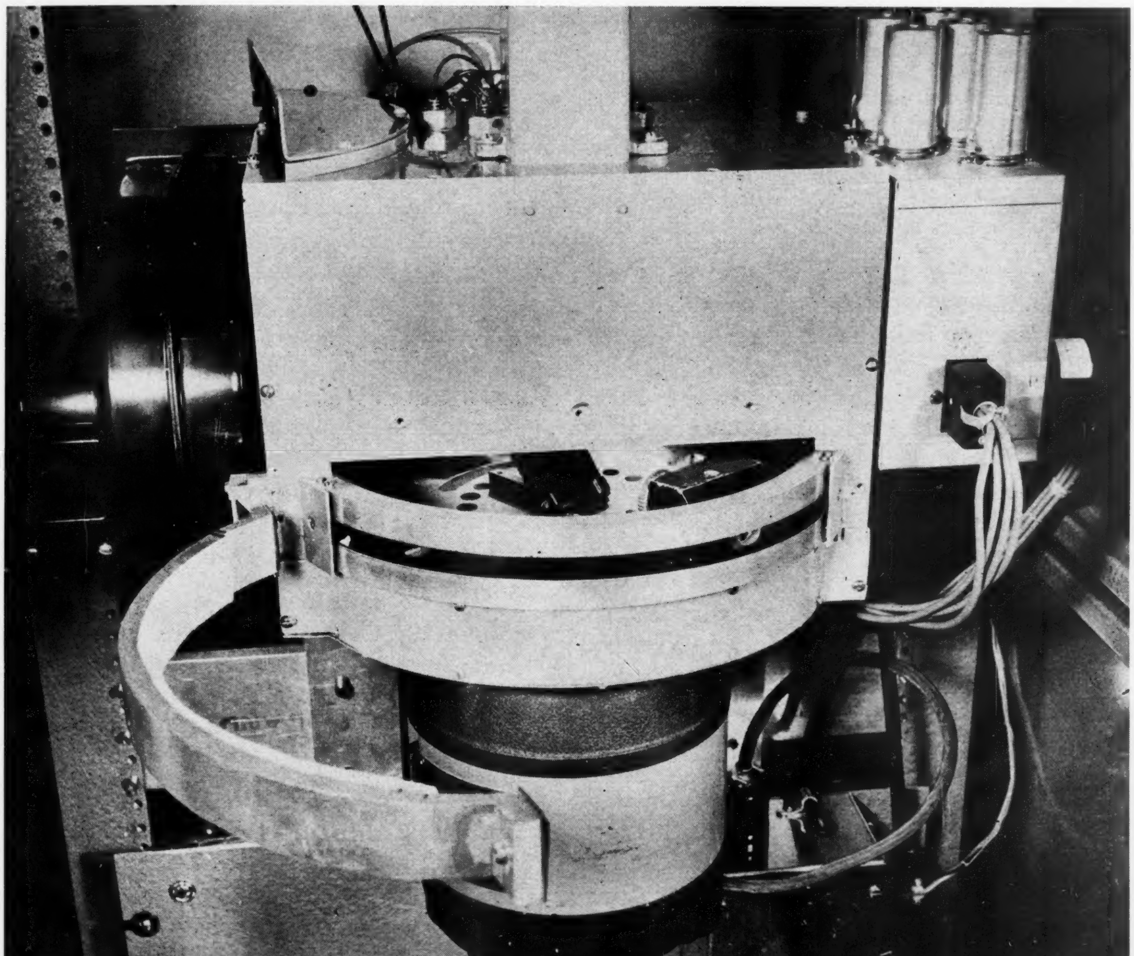

Fig. 5. Close-up of scanning unit with guide bar drawn aside. A portion of the scanning disk (Fig. 6) with slots and centrally placed mirror can be seen through the scanning slot.

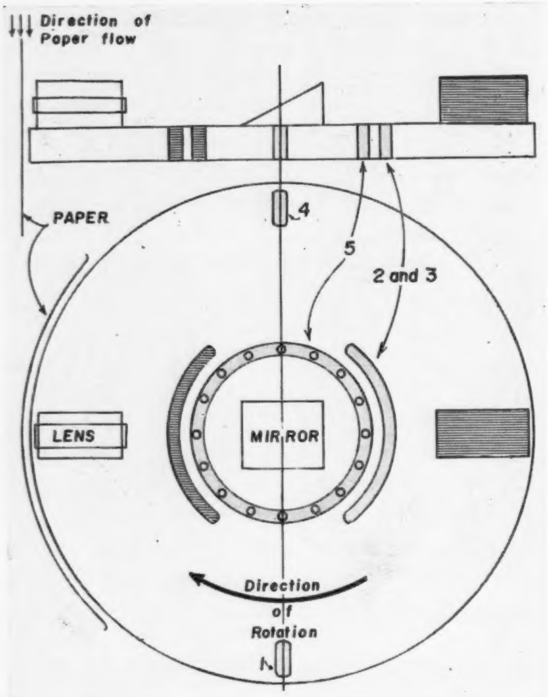

Fig. *6*. Diagram of scanning disk viewed from above and in cross section. Areas that are filled in with parallel lines represent counterbalancing weights and slots. See text for description of purposes of slots numbered *1* to *5*.

ameter, first in *X* area, then in *Y* area. Slot *4* has to do with the mechanism for instructing the machine to print a finished calculation. The ring of circular slots is concerned with holding the counting rate at precisely 1.65 machine units per millimeter. The counting is accomplished by a pulse generator situated between the photomultiplier tube and the computer.

The computer

Fig. 4 shows the computer (to the left of the scanner) with logic, multiplier, accumulator, and printing compartments arranged in that order from above downward under the control panel and oscilloscope.

The *multiplier* accepts impulses from the photomultiplier tube in the scanner unit and multiplies *X* and *Y* diameters. The result is transmitted to the accumulator, which sums and stores the results. After the final scan, the stop mark on the slotted paper signals the logic compartment, which, in turn, activates the printer. Scanning errors are also noted by the machine and summed on the final printed tape. The scanning operation can be easily followed on the oscilloscopic screen.

Accuracy of operation

Theoretically, the only errors possible in the system are those which result from faulty scanning, which, in turn, results from improper tracing, extraneous marks on the paper, or faulty placement of operational marks. The possibility of error due to faulty synchronization (and change in counting rate) is rendered very remote by the inclusion of a device to maintain a fixed relation between the pulse generator and the rate at which the disk revolves (which is synonymous with the rate of scanning).

Tests of accuracy, in which spheres and other objects are used, suggest that the machine does the job most reliably. For spheres, the percentage of error attributable to the machine is slightly over 1 per cent (Table I). For a cylinder with a conical tip which was rotated before the cinecameras (Table II), most of the error is introduced by the method itself and not by the machine. Both the laborious Simpson's rule technique and the calculation from the same tracings by the scanner-computer overestimate the true volume of the object (by as much as 12 per cent). Comparison of the two techniques of measurement, however, shows that the machine is at least as good as human operators and much faster. Much the same can be said when a model of the left ventricular cavity is tested.

Table I. *Comparison of calculated (actual) volumes of spheres and their volumes as determined by cinefluorography and use of the scanner-computer**

Radius (cm.)	*Calculated volume (ml.)*	*Computer volume (ml.)*	*Difference (per cent)*
1.5	14.12	14	−0.86
2.0	33.51	33	−1.54
2.5	65.45	64	−2.26
3.0	113.10	111	−0.89
3.5	179.59	178	−1.16

*The instrument tends to underestimate volume slightly.

Table II. *Results using models (above) and casts (below) of left ventricular cavity**

	Position	Volume (ml.)			
		Actual	Simpson's rule	Scanner-computer	Difference (per cent) (Simpson's rule compared with scanner-computer)
Cylinder with conical tip	1		181.0	182	+0.54
	2		197.0	201	+1.99
	3	178.5	205.2	208	+1.34
	4		202.7	201	−0.84
	5		196.4	194	−1.23
Plaster model of ventricular cavity	1		279	269	−3.71
	2	274	312	315	+0.96
	3		295	303	+2.71

*The cylinder was revolving rapidly when photographed, and positions *1* to *5* represent successive film frames. The plaster model of the ventricular cavity was photographed in three different positions, but was not in motion.

Application

The scanner-computer has been used for calculation of left ventricular volumes in dogs[4] and in man. It also is currently being used to calculate change in volume in aortic aneurysms, giant left atria, and other more-or-less spherical or cylindrical structures. Its chief value is that, by reducing the time needed and the tedium of measurements made on serial x-ray films or on cineangiocardiographic records, it makes a contribution to the use of x-ray techniques for quantitative measurements of circulatory function.

The scanner-computer was designed and built by the National Data Processing Company, 4703 Ross Avenue, Dallas, Tex.

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Movements of the heart during ejection

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Previous reports have dealt with cardiac motions which occur during the pre-ejection phase of systole and during ventricular relaxation.[1,2] The purpose of the present communication is to describe the movements which occur during ejection.

Methods and subjects

The techniques employed were identical with those described in the previous studies. The pressure curves from the four cardiac chambers, from the aorta, and from the pulmonary artery of dogs were differentiated,[3] and the resulting pressure velocity traces were studied in relation to each other and in relation to the precordial movements of normal human subjects. Since each change in slope in the conventional pressure records is reflected in the first derivative by a change in the magnitude of the corresponding deflection, the latter provides more information in regard to the time course of the changes in pressure for comparison with the complex precordial traces from human subjects.

The term *velocity record,* as used in this communication, refers to the first derivative of the pressure curve. These derivative records were recorded at convenient amplitudes and do not represent absolute values.

The precordial records analyzed were the same as those utilized in the previous studies of isometric contraction and of relaxation. Although tracings were made on 50 normal persons from the several V points of the precordium, records from multiple intercostal spaces in a single vertical line were obtained in only 10 subjects. The discussion to follow will deal only with the latter group. The findings in the other 40 subjects were essentially the same.

All precordial tracings were made with the subjects holding the breath at the end of normal expiration. Electrocardiograms (Lead I or II) and carotid pulse tracings (glycerine capsule) were used as timing references.

The terms used in the present report correspond to those in preceding studies. Thus, K_1, K_2, K_4, and K_5 refer to kinetocardiographic tracings as obtained from the corresponding V lines. The second numeral designates the intercostal space from which the tracing was made. Therefore, the term K_{12} indicates a tracing taken from the right second intercostal space, whereas K_{55} refers to a record obtained from the left anterior axillary line in the fifth intercostal space, etc. Tracings from the suprasternal notch are indicated as K_{ss}, whereas the right and left epigastric records are designated K_{er} and K_{el}, respectively.

In the case of records from the right and

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left parasternal and from the left midclavicular lines the "pickup" device was directed in an anterior-posterior direction, and, therefore, downstrokes and upstrokes denote posterior and anterior motion, respectively. The anterior axillary (K_5) traces were also taken perpendicularly to the chest wall, and upstrokes in these may mean either forward or leftward movements. However, in the records from the other regions, the oblique angle of the recording device was such that upstrokes indicate either headward or forward movement (K_{ss} or suprasternal notch), and either footward or forward motion (K_{er} and K_{el}, right and left epigastric regions).

Results

A. Pressure velocity curves of dogs during ejection. The data are summarized in Table I and illustrated in Figs. 1 and 2.

1. THE VENTRICLES AND GREAT ARTERIES. The onset of ventricular ejection was characterized by an abrupt decline in the ventricular velocity trace which occurred simultaneously with the rise in aortic or pulmonic pressure. The velocity records from the vessels soon reached their peaks and began to decline. A small upstroke (Fig. 1, *second arrow*) then occurred in the aortic and, less commonly, in the pulmonary arterial traces. This was sometimes associated with a less prominent upstroke in the ventricular derivative (Table I). The velocity traces then exhibited further reduction, even though the absolute pressures were still increasing rapidly.

As rapid ejection ended, the usual "shoulder" in the ventricular and arterial pressure curves was associated with a continuing decline in their derivatives. The small upstrokes in the conventional pressure records at the onset of the phase of reduced ejection were more clearly seen in the velocity records (Fig. 1, *third arrow*). This phenomenon was observed in every animal and was noted to occur slightly earlier in the ventricular than in the aortic traces.

Throughout the remainder of ejection the velocity records tended to maintain a slow decline, and the aortic curves often exhibited what appeared to be either artifacts or harmonic vibrations of the elastic aortic wall.

Comment: During rapid ejection, the actual ventricular pressures continue to rise. However, and possibly because the opening of the semilunar valves causes sudden enlargement of the total volume in direct communication with the cavities, the *rate of rise* decreases abruptly and the ventricular velocity traces exhibit sharp decline as the arterial upstroke begins. The arterial derivative soon reaches its peak, and the velocity of rise then diminishes, even though the undifferentiated records show that the absolute pressure is still increasing rapidly.

The second small rise in the aortic velocity trace would appear to be of vascular origin because it tended to precede slightly the smaller and less constant increase in the ventricular trace. This deflection is possibly due to elastic recoil of the aortic wall after its sudden distention. As might be expected, this deflection was seen less frequently in the records from the more distensible pulmonary artery. The possibility that it is of artifactual nature cannot be excluded.

The small upstroke which occurred regularly in both the ventricular and the arterial traces at the onset of reduced ejection would seem to be of ventricular origin because it appeared slightly earlier in the records from the cavities than in those from the vessel. Its mechanism will be considered in the later discussion.

2. THE ATRIAL VELOCITY RECORDS. The data are shown in Table I and Fig. 2. During the early part of ejection each animal displayed two abrupt upstrokes in the derivative traces of the two atrial pressures. All dogs likewise displayed two sharp downstrokes in the atrial velocity records. In the latter part of ejection a gradual rise was noted. These various events tended to occur slightly earlier in the right than in the left atrium.

Comment: These several phenomena may be explained as follows: The abrupt upstrokes in the atrial derivatives are probably to be ascribed to headward ballooning of the closed atrioventricular valves, consequent to the high intraventricular pressures. The sharp downstrokes in the velocity records indicate either actual decline or decrease in the rate of rise in pressure in the atria. Such effects

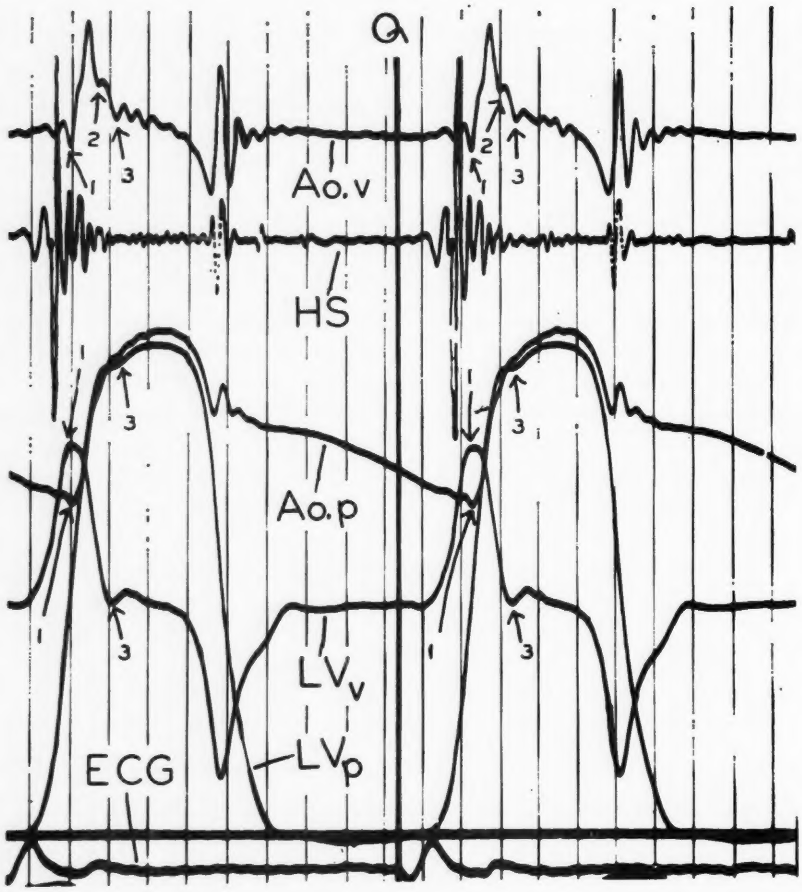

Fig. *1*. The traces of left ventricular (*LV*) and aortic (*Ao*) pressure (*p*) and of the first time derivative of pressure, or pressure velocity (*v*), of a dog are shown during two successive cardiac cycles. The ECG and heart sounds (*HS*) are also depicted. Time lines 0.04 second. Paper speed 200 mm. per second. *1*, The onset of left ventricular ejection is shown by the abrupt rise in the aortic pressure and velocity traces and by the sharp decline in the left ventricular velocity record (*first arrow*). This change is not clearly seen in the undifferentiated LV curve. *2*, The aortic velocity trace reaches its peak about 0.02 second after ejection begins and then declines rapidly. This decline is not smooth but is interrupted by a small upstroke (*second arrow*) which in other animals was sometimes reflected in the ventricular records (Table I). It is possibly due to elastic rebound of the aorta but may represent an artifact. *3*, About 0.05 second after the onset of LV ejection the now declining aortic and LV velocity traces exhibit an increase in the rate of rise in pressure (*third arrow*). This is more apparent in the ventricular than in the aortic record and is present, although less obvious, in the undifferentiated traces. The mechanism of this second rise in pressure is discussed in the text. The subsequent rapid deflections in the aortic velocity trace are not seen in the ventricular record and are probably to be ascribed either to vibration of the aortic wall or to artifacts.

point toward descent of the atrial floor. This might be due either to additional shortening of the papillary muscles or to a further movement (in addition to that which occurs during isometric contraction) of the atrioventricular rings toward the apex. The data supply no evidence as to which of these motions preceded the other.

The slow rise in the atrial pressures during late ejection (V wave) is probably due to filling of these chambers. There is ample evidence that this occurs during ventricular ejection, and it is naturally facilitated by the descent of the closed atrioventricular cusps.

3. RECIPROCAL CHANGES IN THE VENTRICULAR PRESSURE VELOCITIES. It has been shown that during isometric contraction[1]

and during relaxation[2] the two ventricular pressure derivatives often display abrupt changes in opposite directions. Since such changes are probably guides to the movements of the interventricular septum, the velocity tracings recorded simultaneously from the two ventricles during ejection were scrutinized for reciprocal deflections. No consistent tendency toward such was encountered. Such displacement of the interventricular septum as may occur in dogs during ejection would appear to be masked by the other motions which have been considered.

B. Precordial movements during ejection. The findings are summarized in Tables II, III, and IV and in Fig. 3, and are illustrated in Figs. 4 and 5.

I. SIZE OF THE LARGER MOTIONS. The total amplitude of the precordial excursion

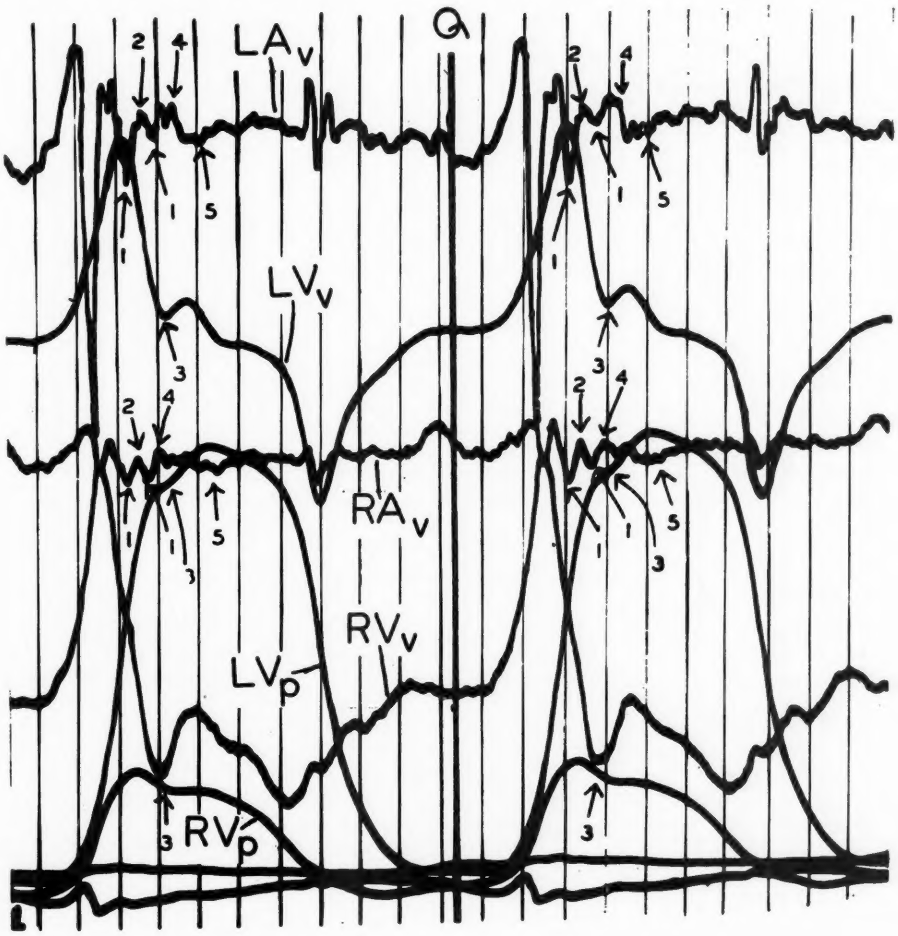

Fig. *2*. Conventional (p) and velocity (v) pressure traces from the four cardiac chambers of a dog are shown during two successive cardiac cycles, beginning and ending at the onset of ventricular excitation. Time lines 0.04 second. Paper speed 200 mm. per second. The onset of ejection of each ventricle is shown by the large downstroke in the respective velocity records. Shortly after the beginning of left ventricular ejection, each atrial velocity trace displays two abrupt upstrokes (*1*), separated and followed by downstrokes (*2* and *4*). These might conceivably be artifacts, but the close correspondence to the precordial deflections in records from human subjects (*see text*), and the constancy of occurrence of one or more of these deflections in the records from different dogs at the same time in the cycle, make this unlikely. The upstrokes are attributed to headward bulge of the atrioventricular cusps, and the downstrokes to further descent of the rings and/or additional shortening of the papillary muscles. The small slow upstroke (*5*), which begins somewhat later, is probably due to atrial filling. As the phase of reduced ejection begins, each ventricular velocity trace exhibits an upstroke (*3*), indicating increased rate of rise in pressure, which may also be seen in the undifferentiated pressure traces. See Fig. 1 and text.

Table I. Summary of changes in pressure velocity in the cardiac chambers and great arteries of

Ventricles and great arteries

Motion	*Left ventricle and aorta*		*Right ventricle and pulmonary artery*		*Interpretation*
	Present in	*Mean time* (sec.)*	*Present in*	*Mean time* (sec.)*	
Arteries ↗ Ventricles ↘	All	0	All	Variable†	Onset of ejection
Arteries ↘	All	0.016	All	.023	Peak velocity of rise in pressure
Arteries ↗ Ventricles ↗	All 5 of 6	0.021 0.024	2 of 5 2 of 5	.025 .025	Elastic rebound or artifact
Ventricles ↗ Arteries ↗	All All	0.036 0.044	All All	.044 .047	Laplace effect? (see text)

*Time after onset of left ventricular ejection.
†Right ventricular ejection either before or after left ventricular ejection.
‡Uncertain whether shortening of papillary muscles or pull of superficial muscles on A-V rings is responsible for this movement.

Table II. Mean times and amplitudes of larger movements during rapid ejection

Movement		*Right parasternal*		*Left parasternal*	
		Upper ($K_{12,\ 13}$)	*Lower* ($K_{15,\ 16}$)	*Upper* ($K_{22,\ 23}$)	*Lower* ($K_{25,\ 26}$)
Total amplitude of trace (mm.)		15.4	22.8	17.5	27.8
Large outward motion	Time (sec. after Q)	Absent	Absent	0.110	0.105
	Size (mm.)	——	——	2.2	6.0
Large inward motion	Time (sec. after Q)	0.111	0.115	0.143	0.136
	Size (mm.)	11.6	16.6	7.2	20.2

and the size of the major deflections are shown as averages in Table II. It will be seen that the degree of excursion was greatest in the lower precordium, and tended to be larger in the left parasternal than in the other areas.

II. GENERAL CONFIGURATION OF RECORDS. The traces from the lower left precordial regions resembled ventricular volume curves in most respects. Records from the right parasternal areas were rather like atrial pressure curves. Deflections from the suprasternal notch were similar to those of an arterial pulse. These several configurations are illustrated in Fig. 4.

A considerable variability in general contour was encountered in the traces from the upper left intercostal spaces. In most

dogs during ejection

Atria					
Motion	Left		Right		Interpretation
	Present in	Mean time* (sec.)	Present in	Mean time* (sec.)	
First ↗	All	.004	All	0.002 before	Bulge of A-V cusps
First ↓	All	.016	All	0.008	Descent of A-V cusps‡
Second ↗	All	.027	All	0.025	Bulge of A-V cusps
Second ↓	All	.038	All	0.032	Descent of A-V cusps‡
Late slow ↗	All	.073	All	0.064	Atrial filling

Mid-clavicular		Anterior axillary		Epigastric (K_{er}, K_{el})	Suprasternal (K_{ss})
Upper ($K_{42, 43}$)	Lower ($K_{45, 46}$)	Upper ($K_{52, 53}$)	Lower ($K_{55, 56}$)		
14.3	20.9	12.7	10.2	19.2	13.1
0.111	0.104	0.118	0.110	See Table III	0.116
4.6	9.3	5.2	4.9	——	7.6
0.156	0.145	Variable (0.18–0.32)	Variable (0.15–0.25)	0.139	Absent
6.1	14.1	Variable	Variable	15.0	Absent

instances, records from the second intercostal space in the anterior axillary line (K_{52}) were of the "arterial" type (Fig. 4,*F*). This configuration was found less frequently in the K_{53} region, and was occasionally seen in the upper (second and third) intercostal spaces in the midclavicular and left parasternal lines. More commonly, the records from the latter areas were of a mixed type; they had some of the features of arterial pulse tracings and resembled ventricular volume curves in other respects.

III. SPECIFIC DEFLECTIONS. The several movements which were commonly observed during the period between 0.08 and 0.105 second after the onset of the QRS, i.e., between the beginning of right and of

Table III. *Precordial motions during period from onset of left ventricular ejection to start of*

Motion	*Frequency of occurrence*	*Time of onset after Q (sec.)*
Large outward of left lower precordial area	Lower K_4: Constant	0.104 (0.09–0.12)
	Lower K_5: Constant	0.110 (0.08–0.14)
	Lower K_2 (29 of 30)	0.105 (0.08–0.12)
	K_{e1} (8 of 10)	0.103 (0.09–0.12)
K_1: Large inward	K_1: Constant	0.112 (0.085–0.14)
Outward of suprasternal and upper precordial areas	Suprasternal: Constant	0.116 (0.10–0.14)
	Upper K_5 (19 of 20)	0.118 (0.10–0.14)
	Upper K_4 (19 of 20)	0.111 (0.09–0.13)
	Upper K_2 (17 of 20)	0.110 (0.085–0.13)

*Size of motion relative to the total amplitude of the record in which it occurred.

Table IV. *Systolic movements of precordium in relation to carotid pulse*

Motion		*Time of onset (sec.)*		*Frequency in various areas*
		After Q	*Carotid*	
During rapid carotid upstroke	Main left precordial and epigastric downstroke	0.13 ± 0.03	0.02 ± 0.01 after CU	Constant at lower K_2 and K_4; variable at K_5
	Small right parasternal upstroke	0.18 ± 0.04	0.06 ± 0.03 after CU	Constant K_1 high Frequent K_1 low Absent elsewhere
During reduced ejection	General outward motion	0.215 ± 0.035	0.09 ± 0.02 after CU	K_1 constant K_E: Almost constant Others: Frequent
	Late inward motions	0.26 ± 0.05	0.15 ± 0.05 before CIN	K_2 constant in one or more areas K_E: Almost constant
	Inward motion of supracardiac area	Variable	Variable	K_{ss}: Constant K_{52}: Usual $K_{53,\ 42,\ 43}$: Occasional

CU: Onset of carotid upstroke. CIN: Carotid incisural notch. K_E: Epigastric traces. K_{ss}: Trace from suprasternal notch.

carotid upstroke

Amplitude		*Remarks*	*Tentative interpretation*
Absolute	*Relative**		
Large	Greatest at K_{45} (apex); K_{55}; K_{56}	Absent at K_1	Forward-leftward-footward recoil of left ventricle
Largest lower K_1	Largest upper K_1	K_2, K_4, K_5: Previous outward motion continues	Decrease in volume due to ejection of both ventricles
Largest at suprasternal and K_{52} areas		Present at K_1 in only one subject	Expansion of great vessels and/or bulge of mitral cusps

Relative size in different areas	*Remarks*	*Tentative interpretation*
Low > high $K_2 > K_4$ K_E: Large	Roughly parallel to stroke volume	Volume change in ejection
K_1: High > low	Often fused with next and larger outward motion	Bulge of tricuspid valve into atrium
K_1: High > low K_5: Low > high	About 0.01 sec. after end of rapid ejection. Often less in fourth than in higher or lower intercostal spaces	Atrial filling (K_1); also descent of inferior border (K_E). Descent of mitral leaflets?
Low > high	Variable small deflections at K_1, K_4, K_5	Volume change in ejection. Terminal shortening of LV with backward, headward pull and decreased base-apex length
Low: Absent	Large relative size	Vascular runoff: (? also pull on semilunar rings?)

LV: Left ventricle.

left ventricular ejection, respectively, have been discussed in the previous report which dealt with the pre-ejection phase of systole.[1] The motions seen during the period when both ventricles are ejecting are summarized in Tables III and IV. They may be subdivided according to their relation to the carotid upstroke.

a. *Motions between the onset of left ventricular ejection and the start of the carotid upstroke* (*Table III*).

1. *The main outward motion in the lower left precordial region.* Approximately 0.105 second after the beginning of the QRS, an outward deflection was observed in the lower K_4, K_2, and K_6 intercostal spaces (Figs. 3,*A*, 4, and 5). This movement was usually largest in the region of the apex (Table II), as would be expected, since it corresponds to the normal apex tap. It appeared to occur about 0.005 second later in the anterior axillary line than in the lower precordial areas. Aside from deflections due to the ejection downstroke and to filling, this is often the largest movement in the normal precordial trace.

The relationship in time of this motion to the ballistocardiogram and to the carotid upstroke was of some interest. In the older subjects it preceded the latter by approximately 0.015 second, whereas in the younger group this motion occurred about 0.025 second before the start of the carotid upstroke. In a given person this motion corresponded closely to the second portion of the biphasic H-I downstroke of the low-frequency acceleration ballistocardiogram.

This sudden outward motion is reduced in amplitude in many patients with cardiac disease, although those with left ventricular hypertrophy commonly display a larger, more gradual, and longer sustained deflection which starts earlier in the cycle.

This deflection appears to correspond to the onset of left ventricular ejection in the dogs, as shown by the sharp rise in the aortic pressure and velocity traces and the simultaneous decrease in the left ventricular velocity record (Figs. 1 and 2).

Comment: In a previous publication,[4] evidence was presented for the view that this abrupt and large outward motion of the precordium represents recoil as left ventricular ejection occurs. The shorter duration between the onset of this motion and the beginning of the carotid upstroke in the older subjects is attributed to more rigid arteries and shorter pulse wave transmission time.

2. *The largest right parasternal inward motion.* At 0.112 ± 0.025 second after Q, a large downstroke occurred (Figs. 3,*B* and 4,*A*). The absolute amplitude of this movement was greater in the lower (K_{15} and K_{16}) than in the upper (K_{12} and K_{13}) intercostal spaces. However, the amplitude relative to the total excursion of the trace was about the same (Table II).

Comment: This deflection occurs at a time when both ventricles are ejecting rapidly, and is ascribed to the volume change of ejection. It corresponds well in time to the first large downstroke observed in the atrial pressure velocity trace of dogs (Fig. 2). These observations constitute evidence in support of the concept[5] that descent of the tricuspid leaflets is of major importance in the mechanics of right ventricular ejection. It is uncertain whether this motion is due to additional shortening of the papillary muscles or of the superficial fibers, with a downward pull on the tricuspid annulus.

3. *Outward motion in the suprasternal and upper precordial areas.* At 0.10 to 0.14 second after Q (average 0.117) the suprasternal and the upper left axillary traces exhibited outward excursion (Figs. 3,*C*, 4, *E* and *F*, and 5,*E*). The upper K_2 and K_4 areas sometimes displayed outward movements which began slightly earlier (Table III). All of these deflections occurred a few thousandths of a second after the larger left lower precordial outward motion which has already been considered.

Comment: These movements began about 0.01 second before the start of the carotid upstroke. In the suprasternal area this motion was the beginning of the pulse wave contour. This observation suggests that the deflection is related to the systolic expansion of the great vessels. However, the left atrial velocity records of the dogs (Fig. 2) exhibited at this time a sharp upstroke which indicated headward bulge of the closed mitral leaflets. Possibly both of these factors contributed to the outward motion of the upper precordial region as observed in man.

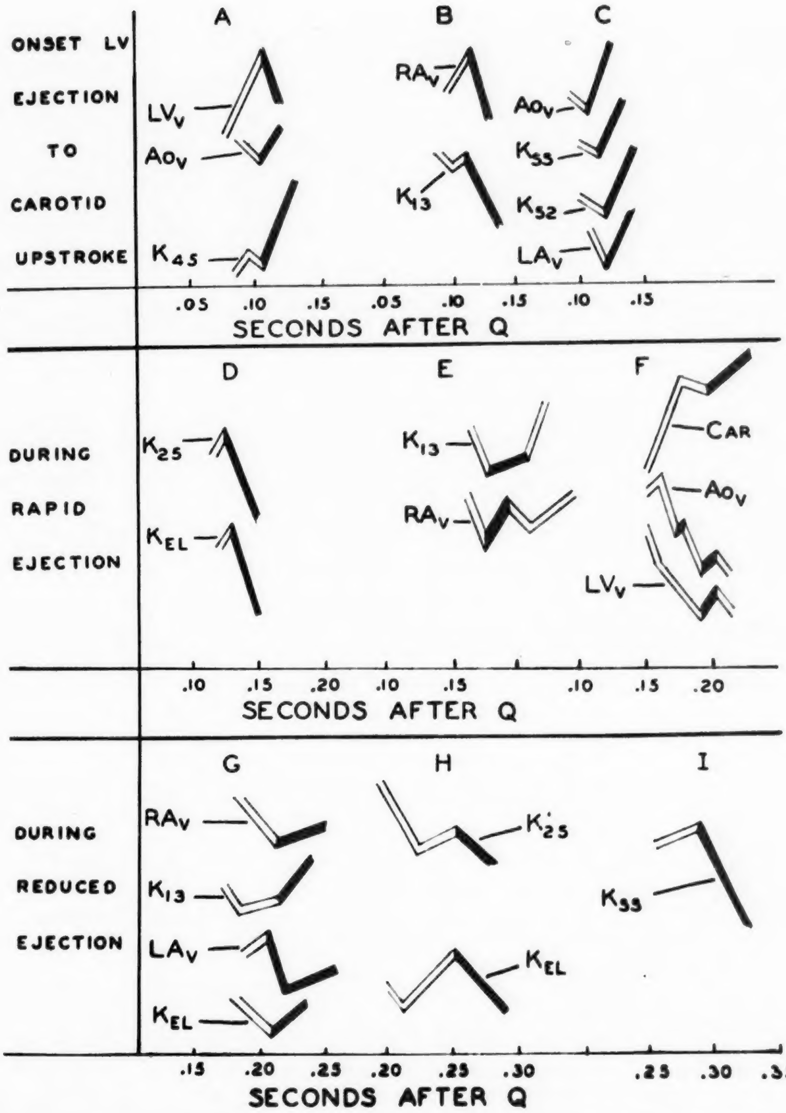

Fig. 3. Diagram of cardiac motions during ejection. The actual times of the pressure velocity (v) deflections of the dogs have been altered to correspond to the same heart rate that was present in human precordial records (K). *A*, Onset of left ventricular ejection is indicated by abrupt respective fall and rise in left ventricular and aortic derivatives of the dog and by a quick outward recoil in the region of the apex. *B*, Large inward motion in the right parasternal region (K_{13}) apparently corresponds to sharp descent of right atrial floor. *C*, Upstrokes in the suprasternal notch (K_{ss}) and in the second intercostal space in the left anterior axillary line (K_{52}) follow the aortic upstroke (*Aov*) by about 0.01 sec., which approximates transmission time of the pulse wave to the aortic arch and subclavian artery. The possibility that headward bulge of the mitral cusps which is regularly seen in the left atrial traces of the dogs (LA_v) contributes to these outward motions of the supracardiac area cannot be excluded. Motions *A*, *B*, and *C* are almost simultaneous. *D*, Large downstrokes over the lower precordium and in the epigastrium represent change in volume. Analogues in the derivatives of the dog's pressure traces occur earlier (*A*). *E*, Upstrokes in the right atrial velocity curve and in the upper right parasternal area (K_{13}) are both ascribed to bulge of the tricuspid leaflets into the right atrium. *F*, The aortic pressure velocity curve displays a small upstroke which is probably due to elastic rebound, and which is sometimes associated with a change in slope in the ventricular velocity record. Just after the end of the rapid ejection these two records and the human carotid (*Car*) trace display upstrokes. These are possibly related to the effect of reduced volume on pressure (see Discussion). *G*, Two different motions are illustrated. The outward motion in the left epigastric area (K_{el}) coupled with abrupt decline in the left atrial velocity record points toward a change in shape in the left ventricle due to descent of the mitral leaflets. The rise in the two atrial velocity curves associated with a generalized outward motion of the precordium, greatest in the area of the right atrium (K_{13}), suggests that the atria are filling more rapidly than the ventricles are emptying. *H*, The terminal inward precordial motions are ascribed to backward and headward motion of the heart borders. No clear analogues were encountered in the pressure derivative traces of the dog. *I*, The last motion observed in the precordial records was a large downstroke in the suprasternal traces (K_{ss}). This is ascribed to runoff from the aorta.

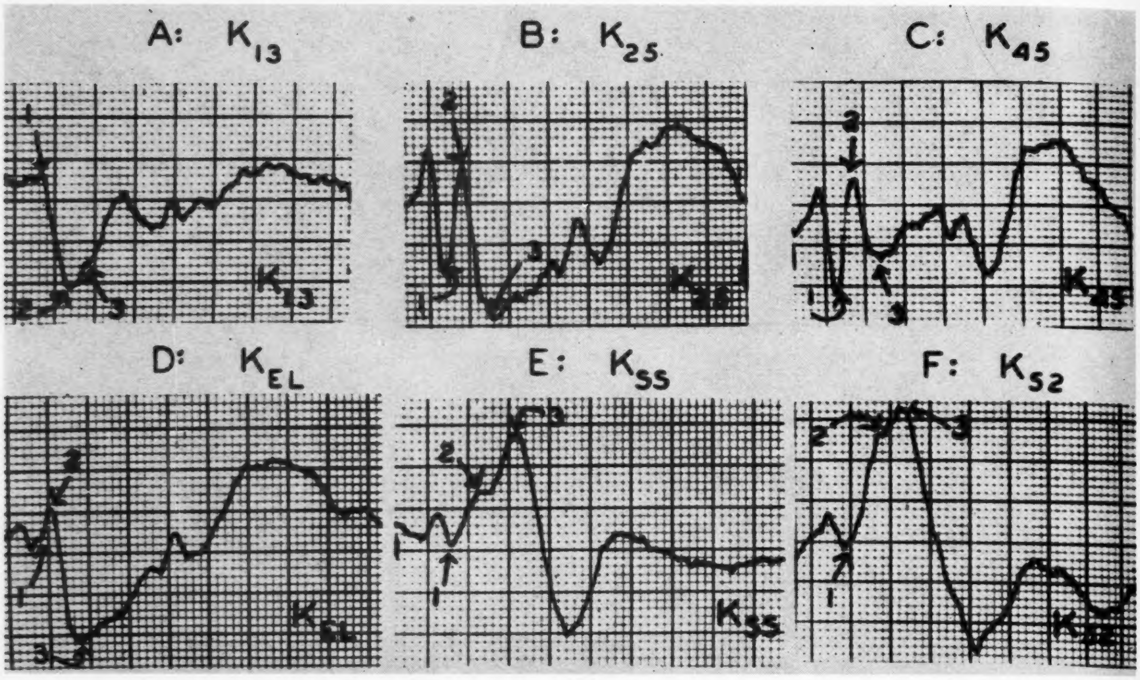

Fig. *4*. D. G., a normal 26-year-old man. Time lines 0.02 second. The traces begin and end at the onset of the QRS. Note the resemblance of the different records to ventricular volume (*B, C, D*), arterial pulse (*E, F*), and atrial pressure (*A*) traces. As left ventricular ejection begins, three phenomena are noted: (1) A large recoil upstroke is seen over the lower left precordium (*first arrow, B* and *C*) and in the epigastrium (*first arrow, D*). In *B* this upstroke is preceded by a much smaller one due to right ventricular recoil. (2) The right parasternal record (*A*) displays a prominent downstroke (*first arrow*), attributed to descent of the tricuspid leaflets. (3) The suprasternal (*E*) and high left axillary (*F*) records exhibit large upstrokes which are attributed to expansion of the aorta and the left subclavian artery, respectively. During the early part of rapid ejection the main inward motion of the left precordial (*B* and *C, second arrow*) and of the epigastric (*D, second arrow*) regions occurs. A little later the small right parasternal upstroke (*A, second arrow*) ascribed to bulge of the tricuspid leaflets is seen. As reduced ejection begins, a large (*A, third arrow*) or small (*B* and *C, third arrow*) outward motion occurs. This is attributed to rapid filling of the posteriorly situated atria. The descent of the inferior border (*D, third arrow*) associated with a downward notch in the upper precordial traces (*E* and *F, second arrow*) is probably due to descent of the mitral leaflets, or of the aortic annulus (see text). The sharp downstrokes in the suprasternal and upper axillary records (*E* and *F, third arrow*) are probably due to runoff of blood from the aorta and from the left subclavian artery.

It may be noted that the three precordial deflections which have thus far been discussed are almost simultaneous. All of these motions (left ventricular recoil, reduction in cardiac volume, and expansion of great vessels) are related to a single phenomenon, the onset of left ventricular ejection.

b. *Motions during the rapid phase of the carotid upstroke*. The abrupt rise in the carotid pulse began 0.11 to 0.145 second after the beginning of the QRS; the average value was 0.126. Rapid ejection, as judged from the carotid pulse, ended 0.17 to 0.25 second after the start of excitation; the average value was 0.205. Both the onset and cessation of the rapid upstroke occurred approximately 0.01 second earlier in the older than in the younger subjects. During this period two precordial deflections regularly occurred (Table IV).

1. *The large left precordial and epigastric downstrokes*. These movements occurred earlier and were larger in the lower than in the upper precordial regions, both in absolute deflection and in relation to the total size of the tracing (Table II; Figs. 3,*D*, 4, *B* and *C*, and 5,*A*). They were somewhat greater in the lower left parasternal than in the mid-clavicular line, and were very variable, both in regard to size and time of onset, in the axillary line. In the epigastric traces this deflection was prominent; the amplitude was about three fourths of the total size of the trace (Figs. 4,*D* and 5,*B*).

Skinner[6] has shown that this deflection is diminished in patients with biventricular failure and usually increases as improvement occurs.

Comment: This large inward motion, which has the greatest magnitude of any single movement during the cycle in some precordial areas, would appear to be clearly related to the volume change of ejection. Its smaller size and later onset in the upper as compared to the lower left precordial intercostal spaces is presumably dependent on the mixture of arterial and ventricular patterns in the upper precordium.

2. *The small right parasternal upstroke.* Shortly before the end of rapid ejection, as judged by the carotid upstroke, outward movement was constantly observed in the right parasternal area (Table IV). In 27 of 49 records from this region a biphasic character of this motion was clearly seen (Figs. 3,*E* and 4,*A*). The first part of this biphasic outward excursion began at 0.14 to 0.19 (average 0.173) second after the beginning of excitation in the K_{12} area, and at 0.16 to 0.22 (average 0.193) in the K_{16} region; the tracings in the other areas were intermediate. The amplitude of this initial portion of the K_1 outward motion was usually small, but the average size was greatest at the K_{12} region and least at the K_{16} area; the intermediate tracings again displayed intermediate values. Since the total amplitude of the tracing during the cardiac cycle was greater in the lower than in the upper regions, the relative size was considerably larger in the K_{12} and K_{13} records than in the tracings from the lower right parasternal intercostal spaces.

The second portion of this biphasic upstroke was much larger than the first. It will be considered later.

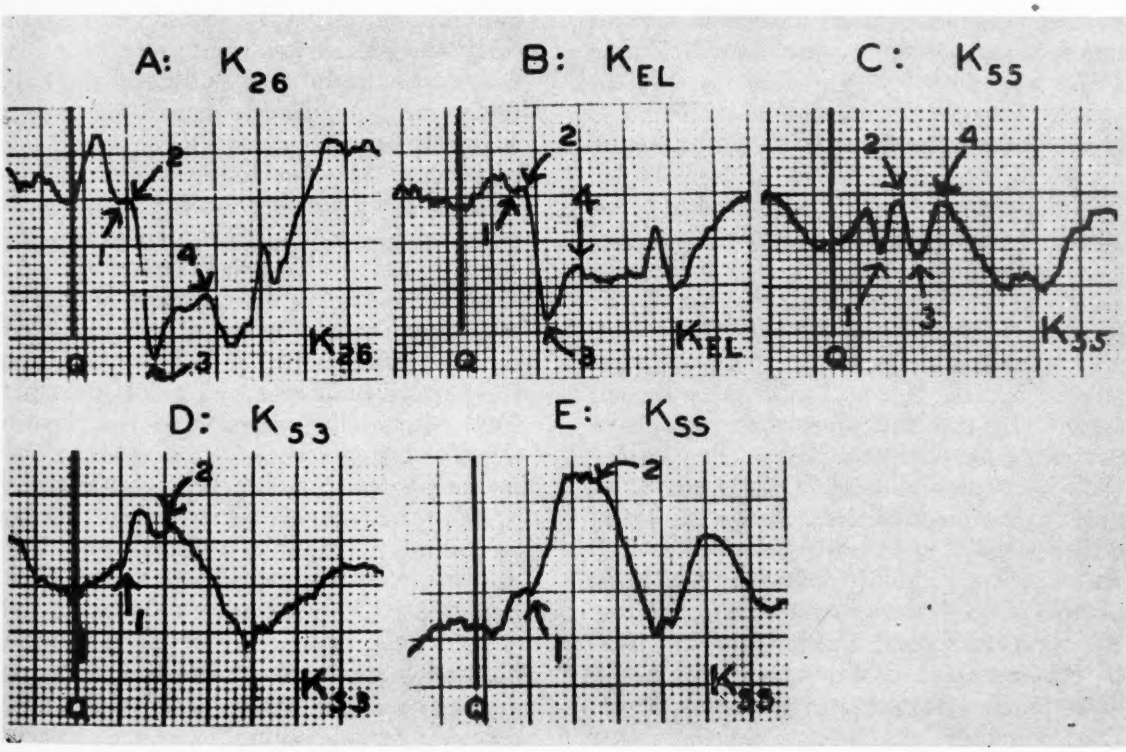

Fig. 5. H. P., a normal 26-year-old man. Time lines 0.02 second. The records begin and end at the onset of the P wave. Q indicates the start of the QRS of the ECG. The recoil movements as left ventricular ejection starts are small in the left parasternal and epigastric areas (*A* and *B*, *first arrow*), but larger in the lower left anterior axillary region (*C*, *first arrow*). The almost simultaneous motions of arterial expansion are readily seen in the high axillary and suprasternal records (*D* and *E*, *first arrow*). The inward motion of ejection is marked in the lower precordial traces (*A*, *B*, *C*, *second arrow*) but not in the supracardiac areas (*D* and *E*). The prominent upstroke in the infracardiac regions (*third arrow*, *A*, *B*, *C*) associated with a downstroke in the upper axillary trace (*second arrow*, *D*) is ascribed to a change in shape as the mitral leaflets are pulled toward the apex. Late in systole, backward and/or headward motion (*fourth arrow*, *A*, *B*, *C*) and arterial runoff (*second arrow*, *E*) are seen.

Comment: The observation that this small right parasternal outward deflection which occurs during the latter part of rapid ejection is consistently earlier and greater over the upper than the lower intercostal spaces in normal persons would suggest that it may be related to some event which transpires in the right atrium. All of the dogs displayed one or more upstrokes in the pressure velocity traces of the two atria at approximately this time of the cycle. The abruptness of these motions make it improbable that atrial filling is responsible. The other possible cause of this precordial motion would appear to be bulging of the tricuspid valve into the right atrium as the pressure in the ventricle approaches its peak.

c. *Motions during reduced ejection.* The rapid phase of the carotid upstroke ends at approximately 0.21 ± 0.03 second after the beginning of excitation. During the next few hundredths of a second, several different movements were noted (Table IV).

1-2. *General outward motion.* At 0.215 ± 0.035 second after Q, or 0.09 ± 0.02 second after the onset of the carotid upstroke, two different movements appeared to occur (Table IV). One of these was a *large outward motion in the K_1 area.* In most subjects the onset of this deflection could be defined (Figs. 3,*G* and 4,*A*), but occasionally it was fused with the preceding upstroke, which began about 0.04 second earlier. In the left precordial region the preceding movement which started earlier than 0.20 second after Q was normally absent, but most of the tracings displayed either a small outward motion (Fig. 4, *B* and *C*) or a sudden decrease in the slope of the inward movement of ejection, at the time the second and larger component of this outward motion appeared in the right parasternal area. In the latter region this movement was greater in the upper than in the lower intercostal spaces, even though the total amplitude of the trace was larger in the latter area. Tucker, Knowles and Eddleman[7] has shown that a movement occurring at the same time as this one is markedly exaggerated in the left precordial area in most patients with mitral insufficiency.

The other motion observed at this time was an *outward deflection in the epigastric region* (that is, forward or downward motion of the inferior border of the heart). This occurred in 18 of 20 records, and was larger on the average than in any of the left precordial areas but was much smaller than the large motion in the right parasternal region (Figs. 4,*D* and 5,*B*). The supracardiac tracings sometimes displayed a small downstroke at this time (Fig. 5, *D* and *E*).

The atrial pressure velocity tracings of the dogs displayed two movements (Table I; Fig. 2) which appeared to correspond to those seen in the human subjects. Aside from the previously mentioned quick upstrokes ascribed to bulge of the atrioventricular cusps, one or more abrupt downstrokes and a later gradual upstroke were observed.

Comment: It would seem that two different mechanisms are responsible for the outward motion which occurs during the early phase of reduced ejection. The descent of the inferior border of the heart (upstroke in epigastric traces) at a time when the ventricles are expelling blood indicates that *the reduction in volume is being masked by a change in the shape of the ventricular cavities.* The decline in the atrial pressure velocity traces of the dogs suggests that the atrial floors (atrioventricular valves) are being pulled toward the ventricles. Additional shortening of the papillary muscles and/or of the superficial fibers which pass from the rings of these valves to the apex would account for the phenomena observed in both species.

The other motion seen at this time was largest to the right of the sternum in the upper intercostal spaces. This suggests that it is related in some way to events which occur in the right atrium. Since Brecher[8] has shown that this chamber fills rapidly during ventricular systole, it seems probable that such filling is responsible for this relatively large outward motion at a time when ejection is still occurring. This conclusion is supported by the finding of a slow upstroke in both atrial velocity traces of the dogs. Because the atria are situated behind the ventricles, atrial filling could likewise account for the small forward motion observed at this time in most of the left precordial traces. The quantita-

tive balance between the respective rates of ventricular emptying and of atrial inflow would determine whether there is an actual outward movement or a decreased inward deflection in the left precordial areas.

The increased prominence of this motion in patients with mitral insufficiency offers further evidence that atrial filling is concerned.

Consideration of the abnormal precordial motions which are commonly seen in patients with cardiac disease is beyond the scope of this communication. However, it may be mentioned that there is evidence, which will be presented in future reports, indicating additional causes of paradoxical (i.e., outward) motion during late ejection in such patients.

3. *Late inward motions of the precordium.* At approximately 0.25 second after the beginning of excitation, and about 0.15 second before the carotid incisural notch, inward excursion of one or more of the K_2 areas was seen in most subjects (Table IV; Figs. 3,*H* and 5,*A*). This was sometimes followed by a small outward motion in the same regions. Downward deflections were likewise encountered in 17 of 20 epigastric traces (Fig. 5,*B*) and in more than half of the records from the K_4, K_5, and K_1 areas.

It is uncertain whether an analogous movement was observed in the dogs. As has been mentioned, all of them displayed an upstroke in the previously declining ventricular velocity traces. However, this change appeared in the animals at a relatively earlier time than the late inward systolic motion of the precordium in the human subjects.

Comment: These motions are probably mainly of left ventricular origin, because they are often exaggerated in persons with left ventricular hypertrophy. It would appear that they are related to terminal contraction of the left ventricle, or of both ventricles, pulling the whole heart or, possibly, the interventricular septum backward and thus causing the inward motion at the K_2 points. Similarly, a headward pull by both ventricles on the inferior border of the heart would account for the downstroke in the epigastric records.

However, since ejection is still proceeding—although at a slow rate—at this time, the distinction between the change in volume of ejection and the postulated terminal changes in shape due to ventricular activity cannot be made with certainty.

4. *Inward motion in the suprasternal notch.* All of the normal subjects exhibited a large late systolic downstroke in the suprasternal tracing, and 9 of 10 in the record from the second intercostal space in the anterior axillary line (K_{52}) (Table IV; Figs. 3,*I*, 4,*E*, and 5,*E*). Such tracings from the second and third left precordial intercostal spaces, which had a general arterial pattern, also displayed a large downstroke at this time (Fig. 4,*F*).

During late systole the ventricular velocity traces of the dogs exhibited a slow decline which was sometimes interrupted by a slight upstroke or by a lessening of the slope of the downstroke.

Comment: This particular motion occurred in records which had the configuration of an arterial pulse wave. When present, it was of large amplitude and corresponded to the late systolic downstroke in the pulse wave record. Therefore, it is to be assumed that this movement was related to runoff from the aorta and, in the case of K_{52} trace, perhaps from the subclavian artery also. The possibility that a terminal downward pull on the semilunar rings also contributed to this deflection cannot be excluded. The tendency toward an upstroke in the ventricular traces of some of the dogs suggests that this may have been an additional, although minor, factor.

IV. SEQUENCE OF MAJOR INWARD PRECORDIAL MOTIONS. Although slight individual differences were noted, a relatively constant general pattern of inward movement was observed (Table II). The upper and then the lower right precordial regions displayed the first main downstrokes. Successive large inward motions were then seen in the lower left parasternal and epigastric areas, the upper left parasternal and apical regions, the upper left midclavicular, the lower left axillary, and the upper left axillary areas. The time of inward motion in the left axillary region varied widely in the different subjects, but in all of them the major downstroke of ejection occurred last in this area.

Comment: These observations indicate that changes in shape are occurring in the

ventricles, even while their volumes are diminishing rapidly. It would seem that while certain fibers are undergoing rapid shortening, others are either shortening more slowly or are actually being stretched. The general sequence appears to be (1) descent of the tricuspid ring, (2) displacement of blood leftward (possibly due to septal shortening), (3) ascent of the apical and inferior margins, with headward displacement of blood, and, finally, (4) inward motion of the lower and then the upper portions of the left border. The relatively sustained outward motion of the left axillary region during the early part of rapid ejection points toward rounding of the left border due to leftward movement of the septum, ascent of the inferior border, and, possibly, downward motion of the mitral ring.

Discussion

The motions observed in the two species appeared to correspond well in most respects but not in all. In the human subjects the three precordial movements (recoil, decrease in volume, and arterial expansion) as left ventricular ejection began were reflected in the respective abrupt rise and fall in the velocity tracings from the aorta and from the left ventricle of the dogs. The descent and bulge of the closed tricuspid valve of the dogs appeared to have analogues in the right parasternal area of the human subjects. An indirect indication of descent of the mitral cusps, in the form of paradoxical (outward) motion of the inferior border, was seen in the human subjects, and direct evidence of such a motion was found in the animals. In both species, evidence of atrial filling was noted during the latter part of ventricular ejection.

No conclusive sign of bulge of the mitral valves was seen in the human subjects, despite the clear evidence for the presence of this phenomenon in the dogs. The motion possibly due to elastic recoil of the aorta in the dogs was not regularly observed in the suprasternal or upper precordial areas of man.

The data appear to offer some elucidation of the contour of the pressure pulse in the ventricles and large arteries. After the "shoulder" which terminates rapid ejection there is a further rise to the highest absolute pressure which is reached during reduced ejection. This late increase in pressure seems to be dependent on cardiac rather than peripheral factors because the corresponding rise in the velocity curve in the ventricles usually precedes that in the aorta and pulmonary artery (Table I). It does not seem probable that additional fibers are entering into contraction, or that there is a sudden increase in the strength of contraction at a time so long after the end of excitation. A more likely explanation of the rise in pressure during reduced ejection is given below.

According to the Laplace equation,

$$\text{pressure} = \frac{\text{tension}}{\text{radius}}.$$

Thus, if the tension, or strength of contraction, remains constant, the pressure will rise as the volume, and hence the radius, decreases. The quantitative significance of this equation will obviously be modified by such factors as the irregular shape of the ventricular cavities, the peripheral resistance, the rate of runoff of blood, and the rebound of the great vessels. However, the principle is applicable, and this explanation is in keeping with the observation that the change in velocity in the ventricles usually preceded that in the great vessels and is, therefore, presumably of cardiac origin.

During ejection, as in isometric contraction, successive areas of musculature appear to reach their contractile peak at different times. The changes in shape so induced may mean that, despite the reduction in ventricular volume, certain fibers are now stretched more than at an earlier phase of ejection. The extent to which the occurrence of such additional stretch in fibers which had previously begun to shorten may cause them to contract with greater vigor is uncertain. There is evidence that such a phenomenon may occur in cardiac muscle.[9] If this effect, which might be called *the secondary length* does, like the initial length, play a role in the force of the subsequent terminal contraction, it may perhaps also contribute to the rise in pressure which occurs during reduced ejection, and, thus, to the contour of the ventricular and arterial pressure pulses. The relation of such phenomena to

the terminal systolic precordial movements is obscure.

These concepts of cardiac motion are in many respects similar to those of Rushmer[10] and his colleagues, who utilized entirely different methods. The observation that the phenomena observed in two separate species studied under varying experimental conditions and with completely different techniques are susceptible to the same interpretations increases the likelihood of the validity of the general concepts. On the other hand, this evidence in regard to the genesis of the precordial motions is of indirect nature, and studies by more direct methods are desirable. Attempts along these lines are currently in progress.

Summary

The precordial movements (kinetocardiograms) of normal adults during ventricular ejection have been analyzed in relation to the velocity of pressure change in the cardiac chambers and great vessels of dogs. The data point toward the following general sequence of cardiac motion.

A. *During the period between the onset of left ventricular ejection and the start of the carotid upstroke*: Three almost simultaneous precordial movements occur at this time. (1) Left ventricular recoil occurs and produces the normal brief apex tap as the left side of the precordium moves out. (2) As both ventricles eject, there is a large inward motion of the right parasternal region. This is apparently produced by rapid descent of the closed tricuspid valve. (3) The expansion of the aorta produces an outward motion in the suprasternal notch, and sometimes in the upper intercostal spaces. The analogous movements in the dog are the respective rise and fall in the aortic and ventricular pressure velocity curves and a sharp dip in the right atrial velocity record.

B. *During the rapid phase of the carotid upstroke:* (1) The volume change of ejection causes large inward motion of the left precordial and epigastric areas. (2) Outward movement of the upper right parasternal region occurs. This is apparently due to bulge of the tricuspid valve, which is shown in dogs by an ascent of the atrial pressure velocity tracing. (3) In dogs the aortic velocity record, having passed its peak, shows a small upstroke which is possibly an artifact, but which may be due to elastic rebound. A similar motion has not been seen regularly in tracings from human subjects.

C. *During reduced ejection:* (1) A large upstroke in the region over the right atrium, and a much smaller outward movement (or diminished inward deflection) in the left precordial area, is ascribed to atrial filling. (2) An outward motion of the epigastrium, and sometimes of the lower precordium, occurs. This is probably related to descent of the mitral annulus, since the left atrial velocity record of the dogs shows a downstroke at an approximately corresponding time. (3) The terminal precordial systolic movements are somewhat variable but usually include inward motion (further decrease in ventricular volume) of the left precordial and epigastric areas. (4) Since blood leaves the aorta more rapidly than it enters, the tracing from the suprasternal notch moves inward.

The pressure velocity tracings from the ventricles and from the great arteries of the dogs show an upstroke as the phase of reduced ejection begins. This is ascribed to the rise in pressure which results from a decrease in volume when fiber tension is relatively constant (Laplace effect).

During ejection, certain changes in shape occur and appear to cause stretch of some of the fibers. The extent to which such *secondary length* may influence the terminal contraction of these fibers is uncertain.

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Case reports

Aortic atresia
A case report and a review

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The pathologic features of congenital aortic atresia have been well documented, but most previous reports have been characterized by a paucity of associated clinical data.

In this case a full clinical evaluation, which included physical examination, electrocardiogram, vectorcardiogram, phonocardiogram, thoracic roentgenograms, retrograde aortogram, and cardiac catheterization, was possible prior to death, and could be correlated with the pathologic specimen.

Case report

L. J., an 11-day-old Negro female infant, was admitted to the University of Florida Teaching Hospital on Oct. 22, 1960, because of dyspnea which had been present for 1 day. The mother had had a normal gestation and labor. The home delivery, assisted by a midwife, was uncomplicated. Breathing and crying were spontaneous. A cleft lip and palate were noted at birth. Twenty-four hours prior to admission, the infant developed tachypnea, dyspnea, lethargy, and anorexia. Grunting respirations developed a few hours before admission.

The family history was noncontributory.

Physical findings. At the time of admission the vital signs were: flush blood pressures—right arm, 118; left arm, 114; right leg, 116 mm. Hg; pulse, 130 per minute, strong and regular; respirations, 84 per minute; temperature, 36°C., rectally. The weight (3.2 kilograms), length (51.5 cm.), and circumference of the head (35.5 cm.) were all normal for the age of the patient. The general appearance was that of an acyanotic, restless infant with severe dyspnea and tachypnea. A unilateral cleft in the left lip extended to the gingiva and into the hard and soft palates.

No thrill was discernible in the suprasternal notch or over the precordium, but a strong thrusting right ventricular heave was palpated at the second and third left intercostal spaces. A Grade 3/6 holosystolic decrescendo murmur, maximal at the fourth left intercostal space, but well transmitted to the apex, base, neck vessels, and left back, and a Grade 1/6 apical mid-diastolic murmur were noted. An ejection click was heard intermittently at the fourth left intercostal space. The second sound in the pulmonic area was very loud and single. The brachial, carotid, and femoral pulses were vigorous and bounding. The lungs were clear to auscultation. The liver was palpable 4 to 5 cm. below the right costal margin.

The remainder of the physical examination gave normal findings.

Laboratory data showed a hemoglobin of 16.4 Gm. per 100 c.c., and a hematocrit of 50 volumes per cent.

Roentgenologic examination (Fig. 1) showed marked cardiac enlargement, a widened superior mediastinum, and prominent convex right heart border secondary to right atrial enlargement, an upward turned apex, and complete filling of the retrosternal space by right atrial and right ventricular dilatation. The pulmonary vasculature was increased and the aorta was not outlined.

There was no roentgenologic evidence to suggest left ventricular or left atrial hypertrophy.

The electrocardiogram (Fig. 2) showed a sinus rhythm at a rate of 130 per minute. The P-R interval was 0.10 second; QRS duration, 0.08 second; Q-T interval, 0.39 second; and the mean QRS axis in the frontal plane, +110 degrees. Right atrial hypertrophy was indicated by tall (0.4 mv.), peaked,

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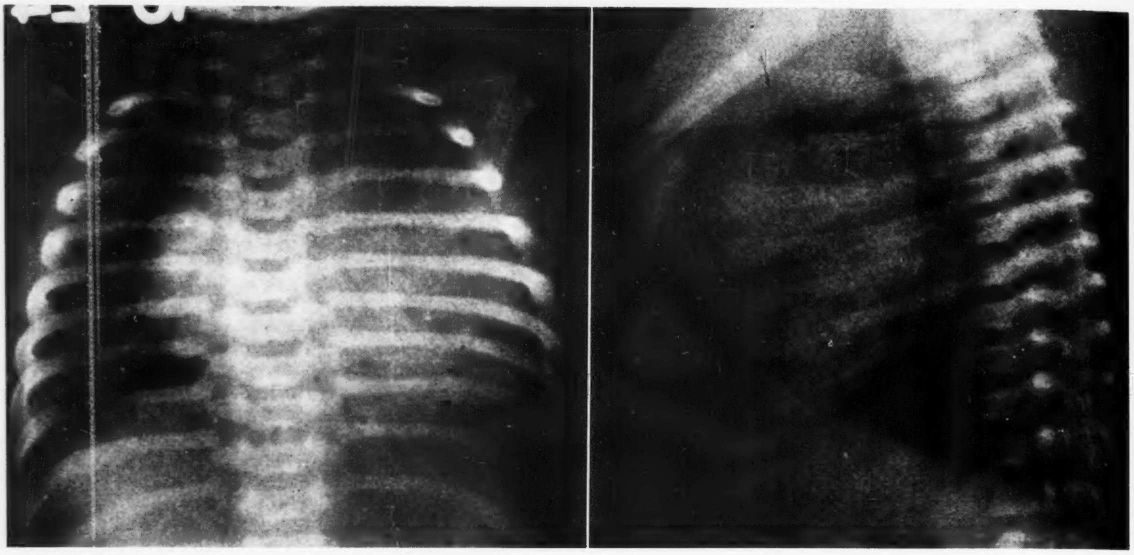

Fig. *1.* Anteroposterior (*left*) and lateral (*right*) thoracic roentgenograms of the 11-day-old female infant who was in congestive heart failure with congenital aortic atresia.

narrow P waves in Leads II and V_2 together with a qR pattern in Leads V_{3R} and V_1. Right ventricular hypertrophy (systolic overload) was indicated by an abnormally high ratio of R to RS (80 per cent) and the qR pattern in Leads V_{3R} and V_1, depressed S-T segments in Leads V_1 and V_2, and positive T waves in the right precordial leads.

The vectorcardiogram (Fig. 2) showed the direction of inscription of the QRSsÊ loop to be clockwise in the horizontal and frontal planes. The initial forces of the QRS vector were displaced posteriorly, superiorly, and slightly to the left. The body of the QRS loop was displaced anteriorly, inferiorly, and neither left nor right. The QRS loop inscribed a very narrow arc in the horizontal and frontal planes, and a wide arc in the sagittal plane.

The QRS-T angle was narrow, which indicated a concordant (normal) relationship of the mean QRSsÊ and TsÊ vectors.

The PsÊ loop was indistinguishable in all planes.

The phonocardiogram (Fig. 3) showed a moderate decrescendo holosystolic murmur, accompanied by a prominent delayed systolic ejection sound (QE time, 0.12 second) which was maximal in the fourth left intercostal space. The first sound was accentuated. The murmur recorded well over the entire precordium. The second sound was single and accentuated. Third and fourth sounds were present at the apex.

A retrograde aortogram (Fig. 4) was diagnostic of aortic atresia. At the time of aortography the oxygen saturation of the blood which was taken from the right brachial artery, with the patient breathing 100 per cent oxygen, was 92 per cent (spectrophotometer, Hickam and Frayser method).

Hospital course. Upon admission, the patient was treated immediately with digitalis, diuretics, and oxygen, and she responded within 24 hours. On the third day of hospitalization, retrograde aortography was performed, and the infant tolerated the procedure well. On the eighth day in the hospital, the respiratory rate increased from 65 to 105 per minute, and the condition of the patient began to deteriorate. She started to have generalized seizures, spells of apnea, and bouts of bradycardia. Cardiac catheterization was performed on the tenth day in the hospital. The patient's condition worsened, and she died during the latter part of the catheterization.

Postmortem examination of cardiovascular system. The pericardial cavity contained about 15 c.c. of a yellowish clear fluid. The heart, which weighed 27 grams, lay in a transverse position, with the apex at the anterior axillary line. The right ventricle was extremely prominent, and the right atrium was dilated approximately two to three times the normal size (Figs. 5 and 6).

The valve of the foramen ovale was competent, but because it was not adherent along the anterior margin, it allowed a 3-mm. opening (Fig. 6). The right ventricle was hypertrophic, and measured 7 mm. in thickness under the tricuspid valve. The septal cusp of the tricuspid valve was cleft. It had gnarled, redundant tissue and was plastered to the inferior margin of a 1-cm., crescent-shaped ostium primum type of atrial septal defect (Fig. 6). The tricuspid valve appeared to be incompetent because of the cleft septal cusp and the dilated orifice of the tricuspid valve, which measured 4.7 cm. in circumference. The other components of the tricuspid valve and the entire pulmonic valve were normal. At the bifurcation of the pulmonary artery was a large patent ductus arteriosus, which measured 5 mm. in width and 2 mm. in length. The pulmonary veins were connected to a left atrium which was normal in size. There was a left atrial-right ventricular communication through the cleft septal leaflet of the tricuspid valve, and a cleft in the hypoplastic mitral valve (diameter of 4 mm.) which lay above the minuscule, 2-mm.-deep left ventricle. The ascending aorta had a normal relationship to the pulmonary artery, but was hypo-

plastic (Fig. 5); it measured 4 mm. in diameter up to the level of the innominate artery, and then was 1.8 cm. in diameter. In the atretic aortic valve, which measured 4 mm. in diameter, three minute, completely fused cusps were discernible. The left and right coronary arteries, their ostia, and their branches traversed a normal course. The great vessels of the aortic arch were normal in diameter and position.

Postmortem examination of lungs. The lungs, which weighed a total of 73 grams, showed extensive atelectasis, grossly. Microscopic sections of the lung showed moderate congestion, extensive atelectasis, scattered petechiae, and had the over-all appearance of "Swiss cheese" emphysema. The arterioles adjacent to the bronchioles were spiral, tortuous, and kinked. The thickness of the pulmonary arteriole wall in relation to total diameter was normal for the infant's age.

The two pertinent diagnoses were: (1) aortic valvular atresia, and (2) ostium primum type of atrial septal defect with cleft tricuspid and mitral valves.

Discussion

Aortic atresia, which falls within the spectrum of hypoplasias of the left side of the heart,[1,2] is thought to be a rare congenital cardiac anomaly. The number of cases reported in the literature seems to approximate 170. However, one is impressed by the divergence of the recorded tabulations; this is caused, in part, by the fact that in the eighteen-eighties the term *atresia of the aorta* had a much broader connotation and included cases of coarctation of the aorta.[3]

Fanfani[4] attributes the earliest report of a case of aortic atresia to Farre, in 1814. This and succeeding reports,[1,3,4-31] were essentially pathologic descriptions. Only in the last few years have clinical studies[2,32,33] been reported in patients with this anomaly.

Theories of the embryogenesis of aortic atresia have been summarized by Sanchez-Cascos and Chiva.[27] There appears to be no correlation with birth weight or any particular prenatal factor. Brekke[25] has reported 2 cases in one family.

Although our patient was a female, several authors[2,4,29,32] have shown that the sex distribution in aortic atresia is approximately 2 males to 1 female.

The early onset of cardiac failure in this infant is characteristic of aortic atresia. Keith and co-workers[32] found this defect to be the most common cause of heart failure in the first week of life.

The cleft lip and palate in our case are not unexpected since additional noncardiac anomalies have been noted to occur frequently in patients with obstructive lesions of the left side of the heart.[2]

Although atresia of the aorta is usually thought of as a cyanotic entity, it is not

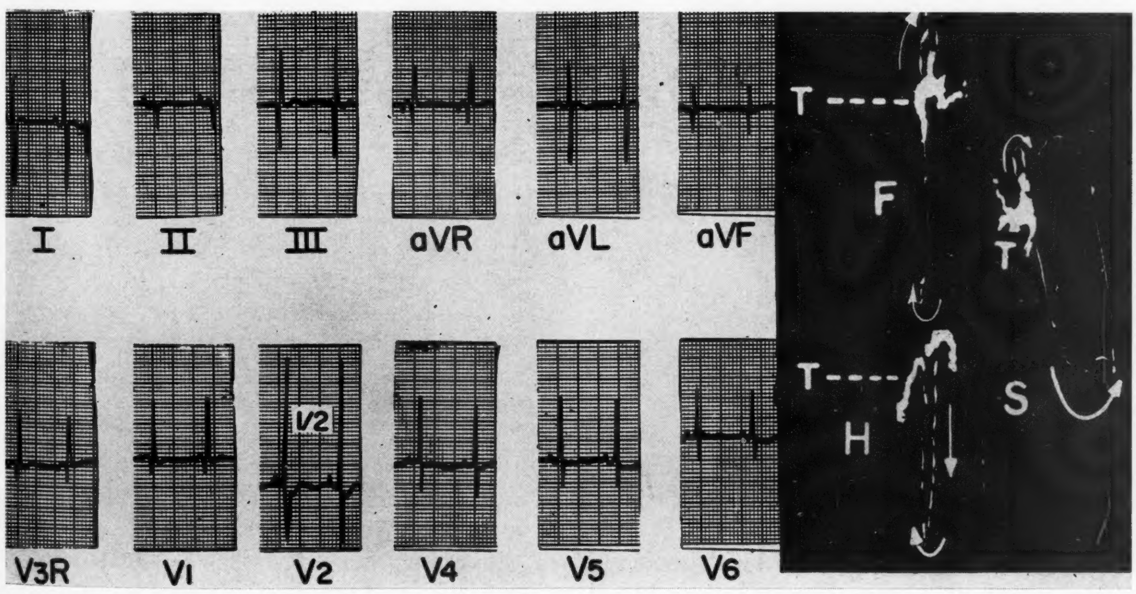

Fig. 2. *Left:* Electrocardiogram of the 11-day-old female infant with congenital aortic atresia (see text for complete description). *Right:* Vectorcardiogram (Grishman cube method) taken when the subject was 15 days old. *H, S, F,* Horizontal, sagittal, and frontal planes, respectively. *T,* T vector loop. Arrows indicate direction of inscription of QRS loop (see text for complete description).

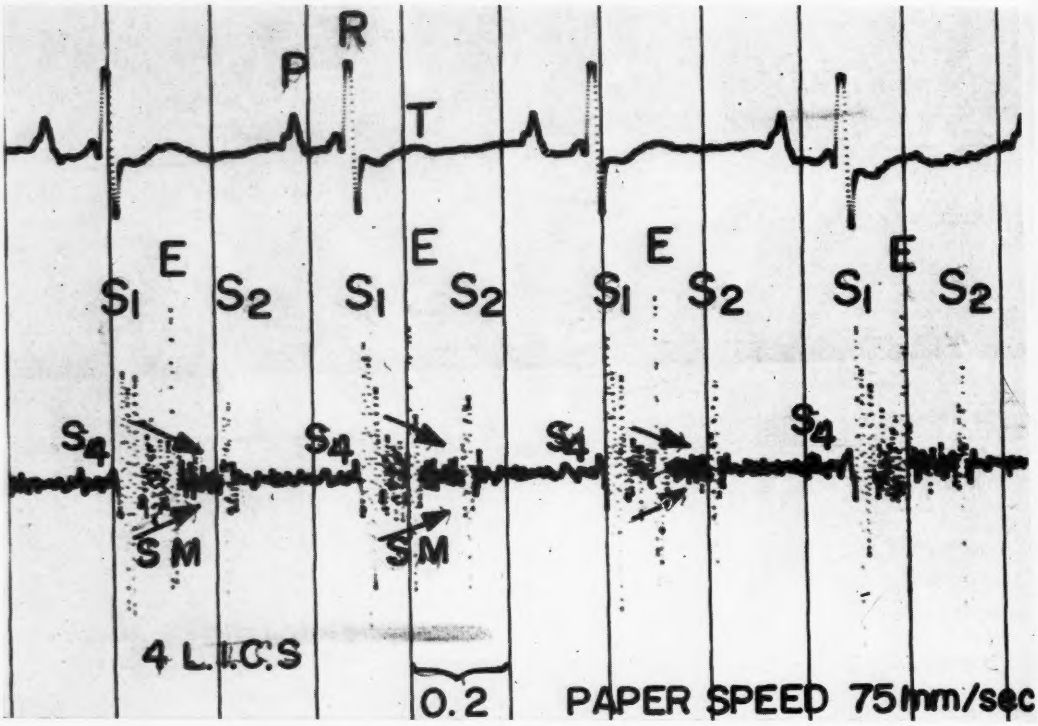

Fig. *3*. Electrocardiographic Lead I (*above*) and simultaneous phonocardiogram (*below*), taken at the fourth left intercostal space in the 15-day-old female infant with congenital aortic atresia. The first sound (S_1) is accentuated. The phonocardiogram shows a moderate holosystolic decrescendo murmur (*SM*) accompanied by a delayed systolic ejection sound (*E*). The second sound (S_2) is single and accentuated. A fourth sound (S_4) was present.

surprising that our patient appeared to be acyanotic. Two separate samples of peripheral arterial blood in our case, with the patient receiving oxygen by mask, were 92 and 87 per cent saturated. Keith and co-workers[32] measured arterial oxygen saturations in 6 cases, and 3 of these had values over 90 per cent when supplemental oxygen was administered. Thus, although cyanosis eventually develops, often in conjection with cardiac failure, it may not be present or clinically apparent in the first few days of life.

The pulses in our patient were vigorous and bounding, with the flush blood pressures over 100 mm. Hg. These are unusual physical findings since Keith and coworkers[32] and Taussig[33] both emphasize the weak or absent peripheral pulses in patients with aortic atresia.

The murmurs described in the reported cases have been variable in location and intensity, and no typical auscultatory findings have been established. Among the 38 infants with aortic atresia reported by Keith, 15 had a systolic heart murmur; the others had none. Ten of the 15 patients in the series of Noonan and Nadas[2] had nonspecific soft systolic murmurs audible over the precordium. In 3 of these 10 patients an additional mid-diastolic rumble over the apex was noted.

Our auscultatory and phonocardiographic findings (Fig. 3) correlate well. The holosystolic decrescendo murmur may be explained on the basis of tricuspid insufficiency or increased flow through the pulmonary valve, or both.

The documentation by auscultation, and the recording on the phonocardiogram (Fig. 3) of a systolic ejection click adds aortic atresia to the list of entities in which this may be noted. Presumably, this systolic ejection sound was caused by rapid expansion of the pulmonary artery. This expansion of the tremendously pulsatile pulmonary artery was documented by cinefluorography and supports the view that the ejection sound was of pulmonic origin. The respiratory rate was too rapid for us to observe whether the intensity of the ejection click decreased with in-

spiration and increased with expiration as is usual when the ejection clicks are of pulmonic origin. The delayed onset indicates a prolonged right ventricular isometric contraction time. The maximum intensity of the ejection click was at the fourth left intercostal space, but it is not unusual for sounds of pulmonic origin to radiate down the left sternal border.

The mid-diastolic murmur at the apex of the heart was presumably due to rapid ventricular filling during diastole, since the right ventricle received the blood from both atria.

Roentgenologic findings, though they at times may be suggestive, are not diagnostic of atresia of the aorta. The marked cardiomegaly (caused by right atrial and right ventricular hypertrophy) and the increased pulmonary vascularity have been reported many times.[2,19,20,23,24,32,33]

The electrocardiogram in this case showed right axis deviation. This was one of the earliest and most frequently described electrocardiographic features,[2,19,23,32,33] although Soloff[20] has reported a case in which there was left axis deviation. Right atrial enlargement, right ventricular hypertrophy, upright T waves in the right precordial leads, with flat to partially inverted T waves in the left precordial leads, were prominent features (Fig. 2), and were also noted by Keith and co-workers.[32] There was no evidence of left ventricular activity over the precordium. Slight slurring of the ascending limb of the R wave, seen in Leads V_5 and V_6 (Fig. 2), can also be noted in Leads V_4 and V_5 in Keith's tracing.[32] The qR pattern in the right precordial leads is an important sign and is consistent with an enlarged right atrium and right ventricle.[35] Although the necropsy specimen showed an ostium primum type of atrial septal defect with "clefting" of both atrioventricular valves, our tracing was not typical of the usual ostium primum defect.[36]

Our tracing showed neither first-degree heart block nor widening of the QRS interval. Lev and Killian[15] accounted for the first-degree heart block in 2 cases of aortic atresia by noting increased connective

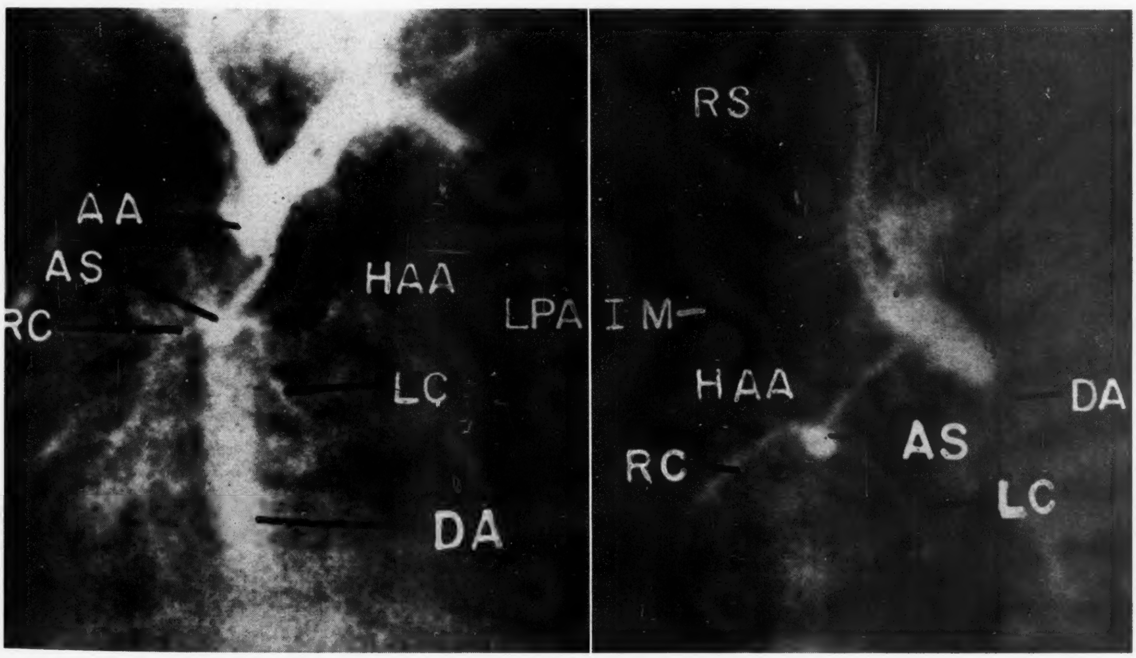

Fig. 4. The retrograde aortogram taken in the 14-day-old female infant with aortic atresia. *Left:* Anteroposterior postion. *Right:* Lateral position. The radiopaque media is seen in the right subclavian artery (*RS*), internal mammary artery (*IM*), and the aortic arch (*AA*). The media is also seen in the hypoplastic ascending arch (*HAA*), a small aortic sinus (*AS*), and the larger right coronary artery (*RC*) and a smaller left coronary artery (*LC*). Another portion of the dye is seen in the descending aorta (*DA*) and the pulmonary arteries (*LPA*, left pulmonary artery). **The media also filled a huge patent ductus arteriosus which is not visualized well in these two frames.**

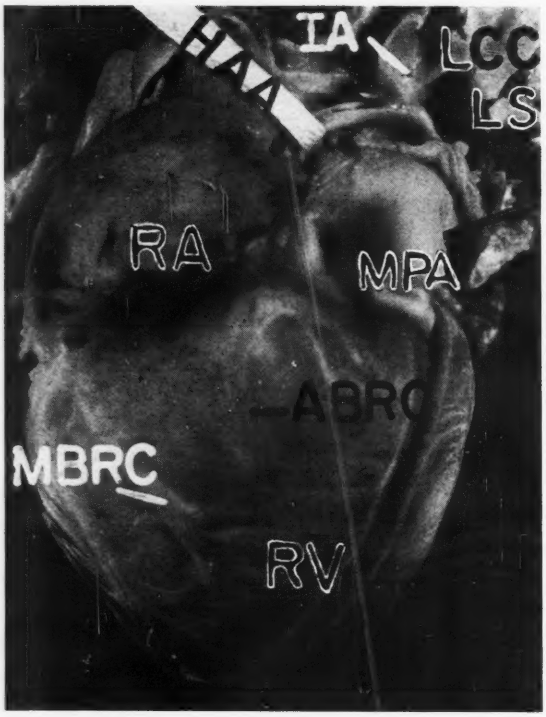

Fig. 5. An anterior view of the specimen at necropsy, showing the very prominent right atrium (*RA*) and right ventricle (*RV*). The hypoplastic ascending aorta (*HAA*) has a normal relationship to the grossly enlarged main pulmonary artery (*MPA*). The great vessels arising from the aortic arch, the innominate artery (*IA*), left common carotid (*LCC*), and left subclavian (*LS*) are normal in size and position. (*ABRC*, Anterior branch right coronary artery. *MBRC*, Marginal branch right coronary artery.)

tissue in the region of the bundle of His. In these same cases there was a prolonged QRS duration, presumably the result of focal degeneration and increased connective tissue in the bundle branches. One of the cases of Friedman and associates[23] revealed left bundle branch block.

In the vectorcardiogram (Fig. 2) the anterior displacement of the T wave in the horizontal plane reveals the basis for the positive T wave in the right precordial leads, and flat to negative T wave in the left precordial leads. The initial QRS forces, directed posteriorly in the horizontal plane, cause the abnormal Q wave in precordial Leads V_{3R} and V_1. The clockwise inscription of the QRS loop in the frontal and horizontal planes is normal for the infant's age. The counterclockwise inscription of the QRS loop in the sagittal plane is usually abnormal, although at times this direction may be observed in normal newborn infants.[36] Anterior displacement of the QRSsÊ loop in the horizontal plane is not abnormal at this age, but the narrowness of the arc and the extreme anterior position are unusual. These findings are consistent with right ventricular hypertrophy.

The aortogram (Fig. 4) demonstrated retrograde filling of the hypoplastic ascending aorta and the large patent ductus so characteristic of this anomaly. The coronary arteries were normally situated, although transposition of these vessels has been reported in cases of aortic atresia.[27]

Retrograde aortography is probably the best and simplest way to establish the diagnosis of aortic atresia. Conceivably, the hypoplastic ascending aorta might not fill with radiopaque media, yet demonstrate the patent ductus arteriosus. In a clinically acyanotic child in congestive failure this set of circumstances might precipitate operation for transection of the patent ductus, particularly when, as in this case, bounding pulses were present.

Forward venous angiocardiography could also be diagnostic, for only in cases of atresia of the aorta would a reverse patent ductus arteriosus fill the ascending aorta.

Physiologic data obtained by catheterization of the right side of the heart (Table

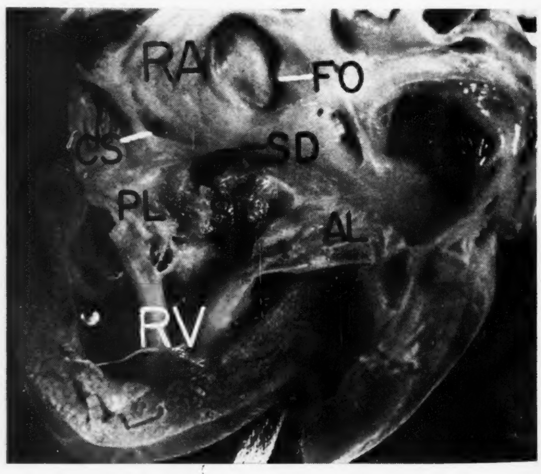

Fig. 6. View of right side of heart, showing huge dilated right atrium (*RA*) and large hypertrophied right ventricle (*RV*). The atrial septal defect (*SD*) is bounded below by the gnarled malformed septal leaflet (*SL*) of the tricuspid valve. *FO*, Patent foramen ovale. *CS*, Coronary sinus. *PL*, Posterior leaflet of the tricuspid valve. *AL*, Anterior leaflet of the tricuspid valve.

I) could be correlated with a majority of our clinical and pathologic findings.

Oxygen saturation in the superior vena cava was very low. This profound degree of desaturation of the systemic venous return probably is a reflection of systemic flow. The large step-up in oxygen content at the right atrial level was produced by the obligatory return of left atrial blood into the right atrium through the patent foramen ovale, or through the septal defect (Fig. 6).

The inferior vena cava and right atrial oxygen saturations were similar, presumably because a stream of blood from the left atrium passed through the septal defect and incompetent tricuspid valve into the mouth of the inferior vena cava. Reflux of blood from the right atrium into the inferior vena cava during contraction of the right atrium may also have been a factor. The pressure in the right atrium was elevated, with a prominent "v" wave, which is compatible with cardiac failure and incompetence of the tricuspid valve.

In this case the right ventricle was the only ventricle which functioned physiologically. The systolic pressure in this chamber, when measured, varied from 35 to 50 mm. Hg. This low pressure is probably a manifestation of the poor status of the patient. The end-diastolic pressure of the right ventricle was elevated, which is consistent with cardiac failure. The right ventricle was the site of maximal arterialization, probably because most of the blood from the left atrium emptied directly into the right ventricle through the septal defect.

Our failure to enter the pulmonary artery made it impossible to evaluate the status of the pulmonary vascular bed. The oxygen saturation of blood which was taken from the left pulmonary vein was less than that taken from the left atrium, right ventricle, and right brachial artery. This paradox might be explained by poor alveolar ventilation in that segment of the lung because of the atelectasis and pneumonia which were noted at necropsy, or by a change in the physiologic state of the infant between samplings.

Table I. *Catheterization data*

*Catheter position**	*Oxygen content*		*Pressures (mm. Hg)*	*Time (sec.)*
	Volumes (per cent)	*Saturation (per cent)*		
Superior vena cava	1.97	18.0		0.0952
Right atrium (mid lateral)	6.38	59.0	Inspiration: 14/4, a = 10, v = 14 Expiration: 32/22, v = 32	0.0935
Inferior vena cava	6.58	61.0		0.0957
Right ventricle (1)	9.31	86.0	35/2 to 12	0.1030
Right ventricle (2)			50/10 to 16	0.1041
Pulmonary vein (1) (left lower)	9.97	74.0	40/7 to 12	0.0944
Left atrium	8.56	79.0		0.1001
Brachial artery	10.79	88.0	80/30, Mean 50	0.1142
PV ⟶ RA			40/20 ⟶ Mean 12	0.0950
PV ⟶ LA			40/18 ⟶ 38/18	0.1000
SVC ⟶ RA ⟶ IVC			Expiration: 22/16 } → Mean 12 → Mean 8 Inspiration: 14/6	0.0953

Oxygen capacity: (1) 10.83 and (2) 12.30 volumes per cent (2 applies to brachial arterial sample only)
Arterial saturation: 87.7 per cent
Systemic flow 0.56 L./min. } Calculated on basis of estimated oxygen consumption of 160 c.c./min./M.^{2}
Index 2.4 L./min.
Resistance 7,140 dynes sec. cm.$^{-5}$

*PV: Pulmonary vein. RA: Right atrium. LA: Left atrium. SVC: Superior vena cava. IVC: Inferior vena cava. Arrows signify pull back of catheter.

The pulmonary venous pressure was elevated, with a distinct pressure gradient between the left pulmonary veins and the right atrium.

The systolic pressures in the right brachial artery were higher than the previously recorded pressure in the right ventricle. Again, these differences must be explained by the changing physiologic state of the infant. The wide variation in pulse pressure (50 mm. Hg) was probably caused by a rapid fall in aortic pressure with ventricular diastole, since, conceivably, the blood in the aorta might re-enter the pulmonary vascular bed.

In aortic atresia, the hypoplastic mitral valve and the minute left ventricle have no functional significance. Many cases of aortic atresia have concomitant mitral atresia.

The systemic cardiac index was slightly below normal values, and again reflects the terminal cardiac failure. Consequently, the calculated systemic resistance was very high.

It has been noted by others[9,23,24] that those infants with the smallest atrial septal defects are the most cyanotic and have the shortest lifespan, presumably because the pulmonary venous return to the right side of the heart is severely compromised. This observation led some to suggest the creation of an atrial septal defect to improve the left-to-right shunt which is essential for survival. As pulmonary flow increases, systemic arterial saturation increases, and, concomitantly, peripheral venous saturation would tend to decrease.

The vast majority of patients with aortic atresia die during the first week of life. The clinical course of our patient was unusual in that the infant lived 21 days. Only an occasional patient has lived longer. DuShane[19] reported a patient who lived 110 days, and Shub and Speer,[24] one who survived 5 months.

Summary

A case of congenital aortic atresia is presented in which the physical examination, electrocardiogram, thoracic roentgenogram, phonocardiogram, vectorcardiogram, retrograde aortogram, and cardiac catheterization were obtained prior to death of the patient at 21 days.

The clinical findings are correlated with the pathologic specimen and compared with the data previously reported in the literature. An unusual anatomic feature was the coexistence of a persistent common atrioventricular canal malformation.

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Hemodynamic observations in a case of carcinoid heart disease associated with an atrial right-to-left shunt

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The cardiac abnormality usually associated with the carcinoid syndrome has been well defined as consisting of an endocardial fibrosis on the right side and associated lesions of the pulmonic and tricuspid valves.[1-4] Cutaneous vasodilation in these patients commonly results in a reddish-violet discoloration of the skin[1,3] which usually can be distinguished with ease from the cyanosis due to arterial oxygen unsaturation. It is not generally appreciated that these types of skin discoloration may coexist, as in the patient now reported upon who had carcinoid heart disease with a right-to-left shunt at the atrial level. This combination is a most unusual occurrence, and, to our knowledge, hemodynamic observations on such a case have not been recorded previously.

Case report

A 50-year-old white married woman had enjoyed good health until 1957, when she developed frequent reddish-blue facial flushes and, eventually, permanent facial discoloration. In 1958, her bowel movements became more frequent, averaging two to five normal-appearing stools daily. Later that year she began to have easy fatigability, dyspnea, palpitations, and slight to moderate dependent edema. She took digitalis leaf, 0.1 Gm. daily for 1 year, without apparent symptomatic benefit. At no time did she have chest pain, cough, wheezing, or orthopnea.

She had never had evidence of acute rheumatic fever, nor were heart murmurs ever detected until 1958. The last physical examination before the onset of the present illness was in 1956, prior to a minor gynecologic procedure.

When she was admitted to the National Heart Institute on Nov. 1, 1960, the temperature was 37°C., pulse rate 76 per minute, blood pressure 125/85 mm. Hg, and respirations 20 per minute. There was a constant, noticeable, reddish-violet discoloration of the face, with a fainter, similar coloring over the upper trunk and the extensor surfaces of the extremities. The fingers were slightly clubbed, with increased mobility of the nail beds. In the jugular veins there were large A waves and very prominent systolic venous pulses. The lungs were clear to percussion and auscultation. The cardiac rhythm was regular. There was a right ventricular heave and a systolic thrill along the left sternal border which increased with inspiration. The first sound at the apex was very faint. A right ventricular diastolic gallop was present. Heart murmurs were graded in intensity on a scale of 1 to 6. There was a Grade 3 blowing, holosystolic murmur over the sternum. A Grade 2 ejection type of murmur was best heard at the pulmonic area (Fig. 1). With inspiration, a faint presystolic rumbling murmur could be heard along the left sternal border in the fourth intercostal space. The liver was palpable 13 cm. below the right costal margin and was firm, nodular, and not tender. No hepatojugular reflux or pitting edema was noted.

No method was found to anticipate or precipitate flushes in this patient. During a flush the pulse rate increased slightly, but the blood pressure did not change significantly. The skin discoloration described above intensified greatly and deep cyanosis of the lips and nail beds appeared.

Laboratory observations included a hematocrit of 49.5 per cent. Normal values were obtained for routine urinalysis, blood urea nitrogen, fasting blood

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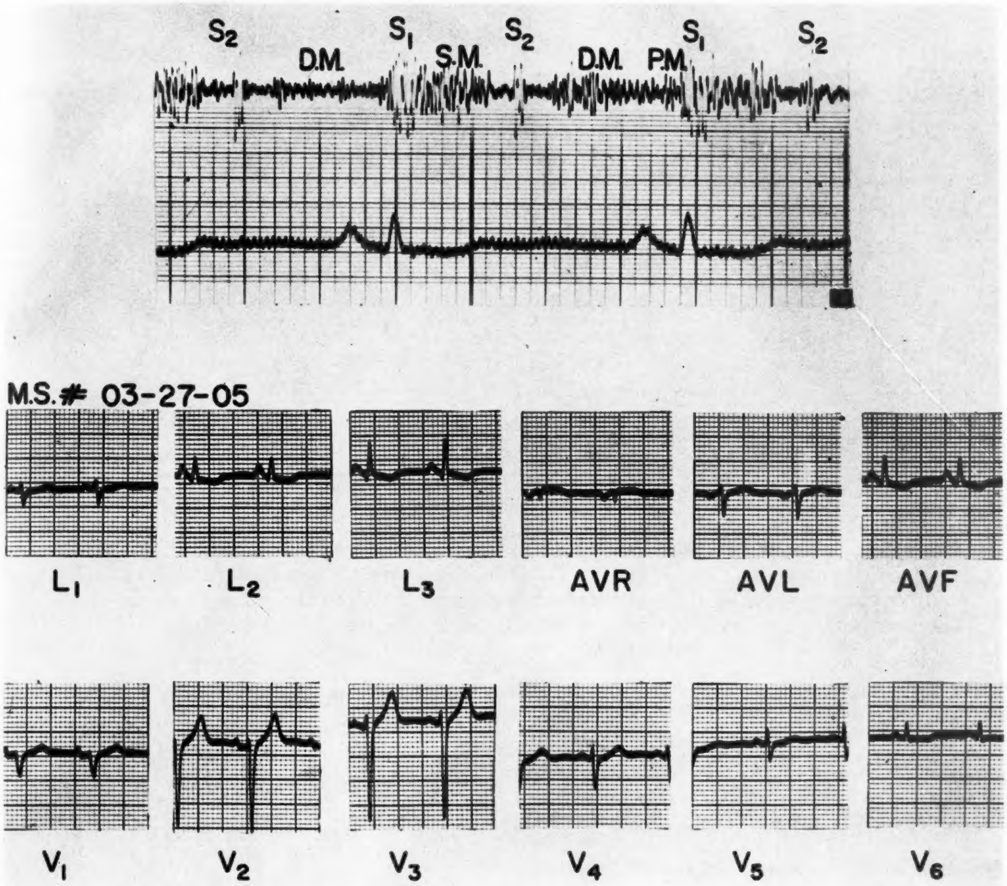

Fig. *1*. Phonocardiogram taken in the fourth intercostal space at the left sternal border. S_1*:* First sound. S_2*:* Second sound. *S.M.:* Systolic murmur. *D.M.:* Diastolic murmur. *P.M.:* Presystolic accentuation of diastolic murmur. Electrocardiogram showing right axis deviation, digitalis effect, and P-wave abnormality compatible with right atrial enlargement.

sugar, white blood cell count, serum electrolytes, total protein, albumin, serology, and serum glutamic oxalacetic transaminase. Average urinary excretion of 5-hydroxyindoleacetic acid on multiple determinations was 396 mg. per 24 hours (normal, 2 to 9 mg.). Liver damage was evidenced by a serum bilirubin of 1.0 mg. per 100 ml., of which 0.9 mg. was indirect, an alkaline phosphatase of 20 King-Armstrong units, and Bromsulphalein retention of 16 per cent in 45 minutes. An x-ray film of the chest showed slight nonspecific enlargement of all cardiac chambers. Multiple small filling defects in the small intestine were visualized on gastrointestinal roentgenograms. An electrocardiogram was interpreted as showing right axis deviation, digitalis effect, and an abnormality of the P wave compatible with right atrial enlargement (Fig. 1).

Catheterization. With the patient lightly sedated, cardiac catheterization was performed through the right saphenous vein. The catheter was passed initially into a peripheral pulmonary artery, where the mean wedged pressure was 4 mm. Hg. The pressure in the main pulmonary artery was 15/8 mm. Hg (mean, 11), and when the catheter was withdrawn into the right ventricle, a systolic gradient of 25 mm. Hg was recorded across the pulmonic valve (Fig. 2). A second catheter with a platinum electrode tip, but also suitable for recording pressures, was then introduced into the right atrium, where the pressure contour was typical of that recorded in cases of tricuspid insufficiency. The mean right atrial pressure was 12 mm. Hg, the A wave was 13 mm. Hg, and the V wave was 18 mm. Hg. Sequential recordings of right atrial and right ventricular pressures revealed a mean diastolic gradient of 9 mm. Hg across the tricuspid valve (Fig. 2). The presence of tricuspid insufficiency was confirmed by the early detection of an indicator substance, ascorbic acid, by the atrial electrode catheter when the indicator was injected into the ventricle.[5] A krypton[85] inhalation test demonstrated that no left-to-right circulatory shunt was present. A platinum-wire electrode was then placed into the left brachial artery through a Cournand needle, and an indicator-dilution curve was recorded after the injection of ascorbic acid into the inferior vena cava (Fig. 3). The early primary curve was formed by the indicator which crossed an intracardiac defect, thereby bypassing the lungs, and the larger secondary curve is the result of the indicator which

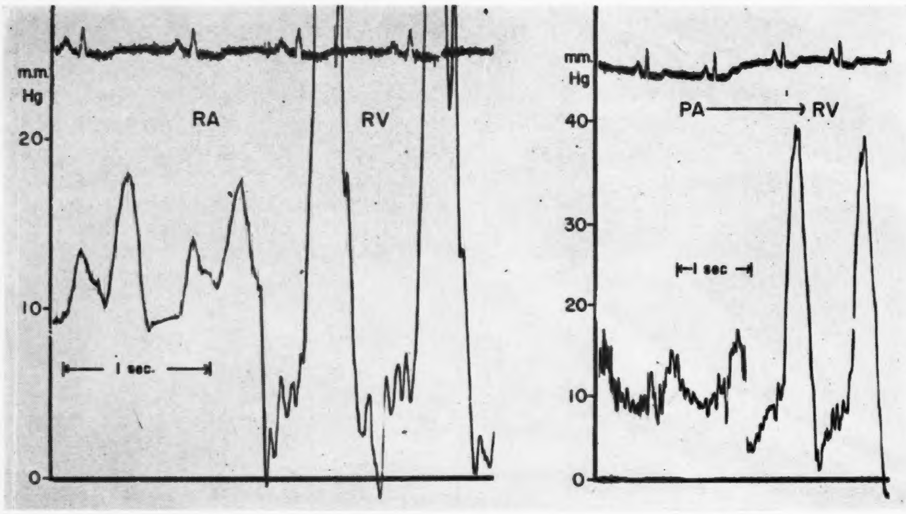

Fig. 2. *Left:* Sequential tracings of right atrial (*RA*) and right ventricular (*RV*) pressures, demonstrating mean diastolic gradient across the tricuspid valve of 9 mm. Hg. *Right:* Pull-out tracing from the pulmonary artery (*PA*) to the right ventricle (*RV*), demonstrating a systolic gradient of 25 mm. Hg across the pulmonic valve.

traversed the pulmonary circulation. When the indicator was injected distal to the right atrium, only the secondary curve was recorded, indicating that the right-to-left shunt was through an interatrial defect. The brachial arterial pressure was 140/85 mm. Hg. The systemic arterial oxygen saturation was 87 per cent at rest and rose to 90 per cent when the patient breathed 100 per cent oxygen for 10 minutes. The atrial septum was probed extensively with the catheter, but the interatrial defect could not be crossed.

In summary, the catheterization findings demonstrated peripheral arterial unsaturation and an interatrial defect with a right-to-left shunt, right atrial and right ventricular hypertension, valvular pulmonic stenosis, and tricuspid stenosis and insufficiency.

Discussion

The catheterization findings of tricuspid stenosis and insufficiency and pulmonic stenosis are consistent with those in cases of carcinoid heart disease previously reported.[6,7] Left heart catheterization was not performed in this patient because she was considered to be too ill to tolerate such a procedure, and because of the absence of clinical evidence of valvular disease on the left side.

The endocardial fibrosis seen in this syndrome is histologically specific and can be readily distinguished from endocardial fibrosis due to other causes.[8] Its cause is not known. The most plausible theory presented, however, is that the hepatic metastases liberate a substance which either directly or indirectly produces fibrosis of the endocardium.[3] It is likely that this substance is serotonin (5-hydroxytryptamine). The scarcity of left heart lesions could then be explained by the abundance of monoamine oxidase in the lungs, which oxidizes most of the free circulating serotonin before it comes into contact with the endocardium on the left side. Sjoerdsma and associates[9,10] were unable to detect significant differences between arterial and venous levels of serotonin, presumably because most of this amine is bound to platelets, and the assay of small amounts in plasma is not feasible technically. It is the free plasma serotonin that is available to be oxidized in the lungs or to produce endocardial disease. Efforts to produce endocardial lesions in experimental animals with serotonin were unsuccessful until

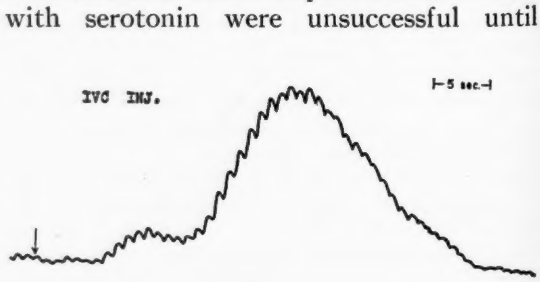

Fig. 3. Indicator-dilution curve after injection of ascorbic acid into the inferior vena cava (IVC), as recorded in the left brachial artery. The early appearance of ascorbic acid is compatible with a right-to-left shunt.

Rossi and co-workers[11] recently infused this amine directly into the ascending aortas of young dogs. The lesions they produced, however, did not resemble, either histologically or by their distribution, those lesions seen in cases of the carcinoid syndrome in human beings.

Fibrosis on the left side may occur in the carcinoid syndrome in the absence of right-to-left shunt, but such lesions are decidedly uncommon and usually quite mild.[3,6,12] The suggestion that the cardiac lesions are entirely secondary to elevations of pulmonary arterial pressure by serotonin is probably untenable since such elevations, although observed experimentally, are not usually seen in the carcinoid syndrome, even during a flush.[7,13]

During a flush, the lips and fingernails of this patient assumed a blue color which was characteristic of the cyanosis of arterial oxygen unsaturation, while elsewhere her skin showed the usual reddish-violet flush of the carcinoid syndrome. There was slight clubbing of the fingers and excessive mobility of the nail beds. These findings prompted us to consider the possibility of right-to-left shunt and to undertake the confirmatory studies outlined above. Because she was previously free of heart murmurs and of cardiac symptoms, we considered this shunt to be through a foramen ovale which had become patent when the acquired valvular lesions caused the pressure in the right atrium to exceed that in the left atrium.

Defects in the atrial septum have been described previously in conjunction with malignant carcinoids. McKusick[14] reported a case, diagnosed at autopsy, with a large patent foramen ovale and fibrosis of all four heart valves. Wolfe and co-workers[15] reported a case with severe valvular lesions on the right side. At autopsy a small patent foramen ovale and mild fibrosis of the mitral valve were discovered. Fischer and Lindeneg[16] presented data derived at necropsy in a case in which a slit-like foramen ovale was associated with fibrosis of all four heart valves and similar mild fibrosis of the coronary arteries. Spain[17] reported upon three cases of malignant carcinoid in which a patent foramen ovale was discovered at autopsy. In none of these cases was there any evidence of valvular or endocardial disease. In the first patient reported by Sjoerdsma and associates,[10] arterial oxygen saturations of 87 to 91 per cent were recorded. The possibility of a small right-to-left shunt through a patent foramen ovale was considered but remained unproved because insufficient data were available. It is surprising that patency of the foramen ovale, which is seen as an incidental finding at as many as 20 to 25 per cent of autopsies,[18] has not been observed more frequently in the cases of malignant carcinoid in which autopsy was performed.

Adherents to the theory that circulating serotonin is the cause of the endocardial fibrosis, and that the rarity of lesions on the left side is due to serotonin oxidation in the lungs, refer to the occurrence of mitral and aortic fibrosis in the presence of communicating atria as a fact supporting this theory. The serotonin-bearing venous blood would thus avoid exposure to monoamine oxidase by direct passage into the left atrium. This study has documented that significant blood flow may occur through such a shunt.

Furthermore, as demonstrated here, cyanosis which appears in the carcinoid syndrome may not always be due to the flush phenomenon. It may be due to arterial oxygen unsaturation, in which case it should be recognized as such.

Summary

An unusual case is presented in which the cardiac lesion of the malignant carcinoid syndrome with pulmonic and tricuspid valvular disease was complicated by a right-to-left shunt at the atrial level, probably through a patent foramen ovale. These findings were documented by right heart catheterization. The probable explanation for the development of this situation is discussed.

We are grateful for the helpful suggestions of Dr. Albert Sjoerdsma, Dr. John A. Oates, and Dr. Eugene Braunwald.

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Clinical pathologic conference

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Clinical abstract

DR. HEATH: The patient whose case is to be discussed was a 51-year-old man who was well, apart from vague attacks of lumbago from time to time, until September, 1953. At that time he had another attack of pain low in the back, which he treated with a lotion. Pain and stiffness developed in the joints, and he began to sweat and feel ill. His general practitioner prescribed aspirin for this, but after a brief abatement of symptoms, the pains in the joints grew worse and a macular rash developed over his body. Six weeks later his eyes began to feel "gritty" and became "blood-shot." He attended an eye hospital, was admitted as an inpatient, and was given atropine and cortisone eye drops. There was some improvement, and therapy with salicylates was continued. One morning, while still an inpatient, he woke up with severe nausea, vomiting, and vertigo. The salicylates were stopped, and phenobarbitone was substituted. He was discharged from the hospital, but developed sensations of irregular beating of the heart. At times he felt as though his heart were stopping. On account of these new symptoms he was admitted to another hospital.

Clinical examination on admission on Dec. 1, 1953, showed him to be a well-built man with a morbilliform rash on the upper trunk and arms. His throat and tongue were clear. The mucous membranes showed no evidence of anemia. No enlarged lymph nodes were palpable. There was an intense inflammatory injection of both conjunctivae. There was circumcorneal injection, and small yellow nodules were present in the sclera. He had swelling and stiffness of the wrists, ankles, and fingers, especially the proximal interphalangeal joints. Examination of the cardiovascular system revealed no pitting edema of the ankles or sacrum. There was no distention of the veins of the neck. The liver was not palpable. The radial pulse rate was 108 per minute, and the rhythm was regular. The systemic blood pressure was 170/90 mm. Hg. The apex beat was palpable in the fifth left intercostal space in the mid-clavicular line. The cardiac impulse was normal. There was a split first sound, a normal second sound, and a loud clicking sound. At one time it was thought likely that he had a faint pericardial friction rub at the apex. The respiratory, alimentary, and nervous systems showed no abnormality on clinical examination. A teleradiogram of the chest was normal.

Investigations. Hemoglobin was 76 per cent (11.3 Gm. per cent). Erythrocyte sedimentation rate (Westergren) was 85 mm. in the first hour. The color index was 0.86. The red blood cell count was 4,400,000/cu.mm. Stained films showed slight anisocytosis, poikilocytosis, polychromasia, hypochromia, and some stippled cells. The direct Coombs test was negative. The white blood cell count was 10,400/cu.mm. The differential count showed: neutrophils 70 per cent, lymphocytes 20 per cent, eosinophils 6 per cent, monocytes 4 per cent. There were no lupus erythematosus cells in peripheral blood, none after a provocative dose of ACTH, and none in bone marrow. The liver function tests were normal. The total serum protein was 6.7 Gm. per cent. Serum albumin was 4.2 Gm. per cent. The serum globulin was 2.5 Gm. per cent. The urine was normal. The electrocardiogram showed sinus rhythm with prolonged P-R interval (0.26 second), early left ventricular preponderance, and T waves which were rather flat in all leads.

Hospital course. Eighteen days after admission he complained of severe discomfort over the xiphisternum which he called "indigestion." Before the nature of this could be discovered, he turned pale, pulseless, and sweaty and collapsed. He died shortly afterward.

Discussion

PROF. ARNOTT: Until September, 1953, this patient had nothing more than the very common complaint of pain low in the back. Then something more definite and crippling appeared. He developed pain and stiffness in the joints and began to sweat and feel ill. This suggests that he had some sort of polyarthritis. I think we must place

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Fig. *1.* Mitral and aortic valve, aorta, and part of wall of left auricle; fibrous thickening of both valves, and upper part of aortic wall; sharply localized bulge in aorta just above aortic valve (elastic–van Gieson).

particular emphasis on the fact that the proximal interphalangeal joints were involved in this case, for this leads one to believe that he had rheumatoid arthritis. He also developed a macular rash; well, the word "macular" just means a spot, nothing more. Strictly speaking, it is applied to a rash which is not raised above the surface of the body, but I think that perhaps we must not be too precise about this interpretation. Six weeks later his eyes began to feel "gritty" and became "bloodshot." The fact that atropine and cortisone drops were used suggests that quite a serious view was taken of this disease of the eyes. If we take the treatment into consideration, together with the description of the lesion, we must conclude that he had something in the nature of iridocyclitis and not a simple conjunctivitis. One morning, we are told, he woke up in the eye hospital with nausea, vomiting, and vertigo. This not uncommon triad of symptoms could mean anything or nothing. The therapy with salicylates was stopped, which suggests that this treatment was having an excessive effect. He then complained of sensations of an irregular beating of the heart. The causes of that are usually extrasystoles, paroxysms of tachycardia, or bursts of auricular fibrillation. At times he felt as though his heart were stopping; these are the sensations of a person who has extrasystoles with a long, compensatory pause. Somebody took a serious view of this symptom because he was transferred to a general hospital. Nevertheless, at this time there was no evidence of congestive cardiac failure. His systolic blood pressure was a little above normal but his diastolic pressure was normal.

Eighteen days after admission there was a dramatic development. He complained of severe discomfort over the xiphisternum, not actual pain, and, before the nature of this could be discovered, he turned pale, pulseless, and sweaty, and collapsed and died shortly afterward. There is one thing which I think that we can accept at its face value without undue suspicion—the fact that he was dead! He didn't die abruptly, he didn't go out like a light, as happens when a person develops cardiac arrest or when he breaks suddenly into ventricular fibrillation and the cardiac output falls to zero in a matter of seconds. This process of dying occupied some time. It suggests to me not a sudden arrest but rather a quite rapid decline in cardiac output. Now what does all this mean? One strives always to solve these problems

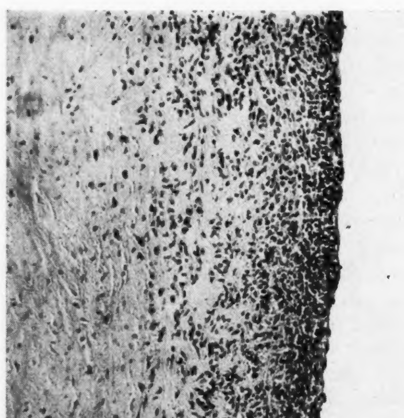

Fig. *2.* Heavy, predominantly lymphocytic and plasma cell infiltration of aortic intima (hematoxylin and eosin, ×100).

Fig. 3. Aortic adventitia, showing a similar heavy cellular infiltration (hematoxylin and eosin, ×100).

on the basis of one logical process. This is not always possible because older people often have more than one disease. Nevertheless, one tries to apply this analytical technique first and this is what I shall attempt to do now.

The onset of rheumatoid arthritis is by no means uncommon in his age group, and it runs a course just like that described in the clinical summary, with swelling of the joints and systemic disturbance to the extent that the patient feels sweaty and ill with fever. Skin rashes are not uncommon, occurring in about 10 to 15 per cent of the patients. The wide variety that may occur include erythema multiforme, as in acute rheumatism, erythema nodosum, or a nondescript macular rash of the type described here. Iridocyclitis is also quite common in rheumatoid arthritis and occurs in the same percentage of cases as do the skin lesions. One type of iridocyclitis which occurs in rheumatoid arthritis is termed "necroscleritis nodosa"; it presents in a manner very similar to that described in the clinical summary.

Now what cardiac disturbances occur in rheumatoid arthritis? Pericarditis is occasionally seen, and in this case a pericardial friction rub was heard at the apex, but, when we come to consider and explain the sudden demise of this patient, we have to broaden our concept of rheumatoid arthritis. This disease is best regarded not so much as a specific entity but rather as coming within a broad group of conditions which merges at one end with the collagen diseases and at the other with polyarteritis nodosa. If one extends the concept of rheumatoid arthritis in the latter direction, and realizes that polyarteritis frequently coexists with the involvement of the joints, we may begin to explain his death. He may have had polyarteritis nodosa of the coronary arteries which led to an aneurysm of one of these vessels. Such an aneurysm may have bled into the pericardial sac; initially, this would lead to intense epigastric discomfort, such as he suffered. There would also have been progressive reduction of stroke volume associated with the filling up of the pericardial sac with blood. Finally, in the course of this "cardiac tamponade," cardiac relaxation would have become impossible and the patient would have died in the manner described. This is the chain of events that I would imagine might have occurred in this case.

Of course, he may have had two common

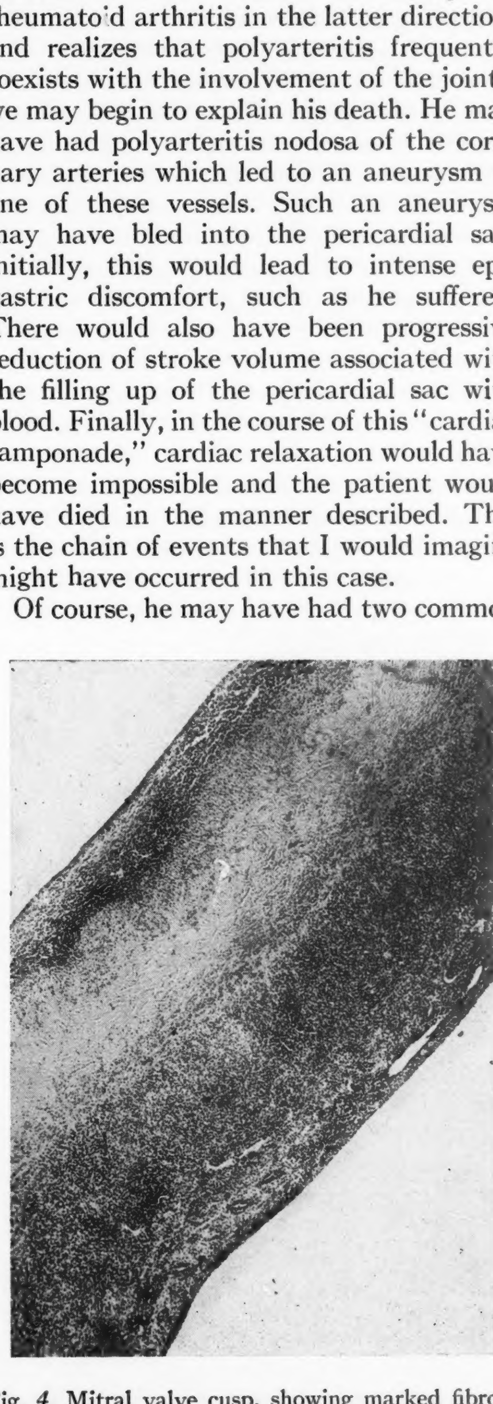

Fig. 4. Mitral valve cusp, showing marked fibrous thickening and very heavy chronic inflammatory cell infiltration (hematoxylin and eosin, ×24).

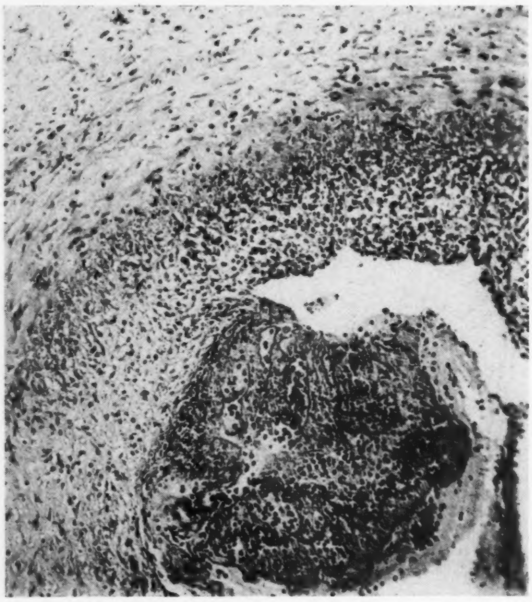

Fig. 5. Coronary artery; fibrosis of intima and adventitia with thrombosis (hematoxylin and eosin, ×150).

diseases. He may have had rheumatoid arthritis and an acute myocardial infarction, which is very much of a possibility, because rheumatoid arthritis does not protect against coronary artery disease, and he was in the sixth decade.

Other remote possibilities include disseminated lupus erythematosus, which is just another member of this same group. Brucellosis may also cause swollen joints (though rarely in the interphalangeal joints), skin rashes, and iridocyclitis but does not cause sudden death of this sort, and it is an uncommon disease in this part of Great Britain. Sarcoidosis can also give rise to pain in the joints, and this disease is, of course, associated very commonly with iridocyclitis. Sarcoidosis can affect the heart and has been known to cause heart block, but in the case under discussion the x-ray film of the lungs was said to show that they were clear, a point very much against this diagnosis. Acquired toxoplasmosis, which is rare in this country, can cause iridocyclitis, pain in the joints, and skin rashes but not sudden death, and there is no particular tendency to cardiac involvement. Coccidioidomycosis is very rare in Great Britain, but it can also give rise to an acute form of illness of this type. The erysipeloid of Rosenbach, acquired from cattle and pigs, may cause erythemata and pain in the joints, but after running a course of 2 or 3 weeks this disease shows a steady abatement. Furthermore, it carries no great cardiac menace and is again very rare indeed in this country.

DR. HEATH: Well, now you have heard Professor Arnott's summary of the case. He believes that the patient has rheumatoid arthritis with iridocyclitis. He thinks that there is organic heart disease, due to polyarteritis nodosa affecting the coronary arteries and leading possibly to an aneurysm of one of the vessels, with subsequent rupture of it and cardiac tamponade.

MR. ABBOT (student): Were any serologic investigations performed on this patient? In particular, I have in mind sheep cell agglutination and the Wassermann reaction.

DR. HEATH: The former was strongly positive and the latter negative. This positive sheep cell agglutination would support your diagnosis of rheumatoid arthritis, Professor.

PROF. ARNOTT: Yes, but of course this test is not quite specific for this disease. It is also positive, for instance, in disseminated lupus erythematosus.

PROF. SQUIRE: Was a blood culture done?

DR. HEATH. No. Would Dr. Brewer now describe the macroscopic findings without giving us his diagnosis.

DR. BREWER: There was an acute inflammation of the sclera and a slight generalized enlargement of the lymph nodes. The rash had faded after death, as it commonly does.

Internally, the most striking changes were in the cardiovascular system. There was a small pericardial effusion of clear, pale yellow fluid. Both ventricles of the heart were enlarged. The tricuspid and pulmonary valves were normal. There were unusual changes affecting the mitral and aortic valves, and the aorta and its branches. The posterior cusp of the mitral valve was normal. The anterior cusp was grossly thickened and fibrous, with a nodular surface. The chordae tendineae were not fused or thickened. There was similar, though less marked fibrous thickening of all cusps of the aortic valve. There was marked fibrous thickening of the

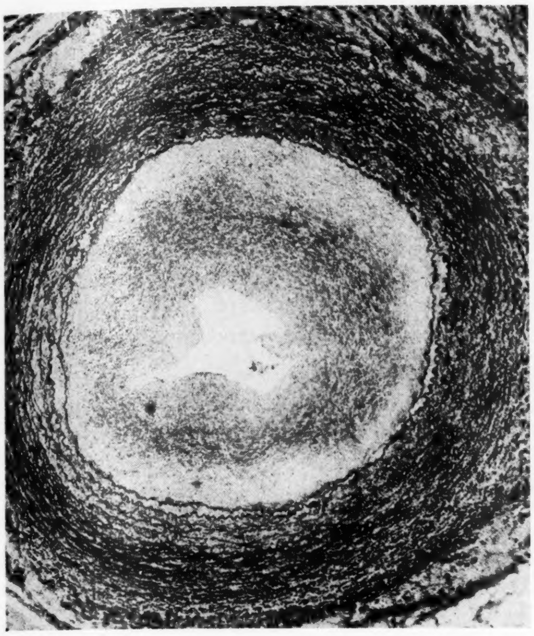

Fig. 6. Gross intimal fibrosis of brachial artery (elastic–van Gieson, ×24).

aortic wall which affected the ascending aorta, the arch, and the thoracic aorta. The intima was slightly nodular. This thickening affected also the large peripheral arteries and the coronary arteries, particularly the left anterior descending branch. In these arteries the thickening was also mainly adventitial but encroached on the lumen, reducing the lumen of the coronary arteries to a pin point in several places. There were small scattered areas of fibrosis in the myocardium but there was no recent infarct. The only other change of note was in the pancreas, in which there were small round areas of fibrosis which I took to be similar changes in the arteries of the pancreas, but, in fact, they turned out not to be.

DR. HEATH: How do you interpret these findings, Professor?

PROF. ARNOTT: I think they are due to rheumatoid aortitis. They are not very common, but changes of this type have been described by my friend Walter Bauer, at the Massachusetts General Hospital, who has described several similar cases.[1,2]

DR. HEATH: Yes, I agree. You will notice that the pathologic findings in the aorta are extremely similar to those of syphilitic aortitis, but Mr. Abbot has already cleared the ground there for us and excluded syphilis because we know that the Wassermann reaction was negative.

Shall we have the histologic findings?

DR. BREWER: The aorta showed fibrous thickening of the intima and adventitia (Fig. 1). In the ascending aorta was a small, sharply localized bulging of the media (Fig. 1). There was a very striking infiltration of the intima (Fig. 2) and adventitia (Fig. 3) by chronic inflammatory cells, with lymphocytes and plasma cells predominating. There was a pronounced histologic resemblance to syphilitic aortitis. The mitral valve also showed a marked fibrosing chronic inflammation with a heavy cellular infiltration of auricular and ventricular surfaces (Fig. 4).

I made this postmortem examination in 1953. At the time I was unable to put a name to the condition. It was only fairly recently, when I read the papers to which Professor Arnott has referred, written by Bauer and his associates,[1,2] that I realized that this case was an example of the condition they describe as rheumatoid aortitis. In those cases there was a chronic fibrosing inflammation of the aorta, of the aortic valve, and, in some cases, of the mitral valve also. In all the cases reported the

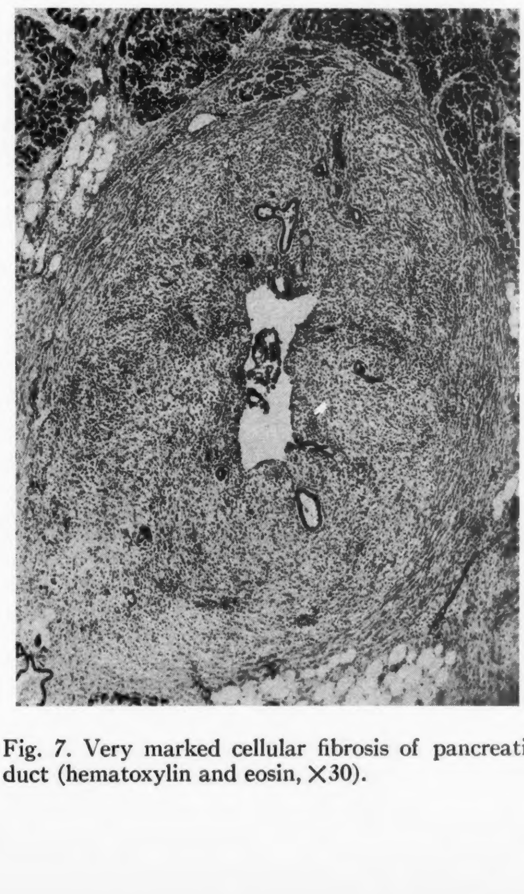

Fig. 7. Very marked cellular fibrosis of pancreatic duct (hematoxylin and eosin, ×30).

Wassermann reaction was negative. In the present case, in addition to the changes in the heart and aorta, there were changes in the peripheral arteries. The left anterior descending coronary artery showed marked intimal thickening adventitial fibrosis and a recent thrombosis (Fig. 5), which I assume accounted for his death. The right main coronary artery also showed intimal and adventitial fibrosis. Of the other arteries examined, the internal, right, and left common carotid arteries were normal. The right and left brachial arteries, the right and left femoral arteries, and the superior mesenteric artery also showed changes. Fig. 6 shows very marked fibrous intimal thickening in a brachial artery, with a very brisk inflammatory response in the adventitia too. The areas in the pancreas that I assumed were small fibrosed arteries were, in fact, ducts that showed a very unusual fibrous thickening (Fig. 7). I have not seen such a change previously, and it has not been described in any of the published cases of rheumatoid aortitis.

PROF. ORR: I would accept rheumatoid aortitis as a pathologic entity. I am rather surprised that Dr. Brewer should have described the changes in the aorta as resembling syphilis, because on the slide that he showed us the media of the aorta seemed to be singularly free from inflammation.

DR. BREWER: There are at some levels a slight infiltration and vascularization of the outer part of the aorta, but I would agree that it is not so extensive as in the case of syphilis. It is only about the outer fourth of the media that is involved at any level. It is predominantly adventitial.

DR. HEATH: With regard to the mode of death I am sure that many of the audience will be familiar with the histologic changes that were present in the myocardium of this patient. They were typical of acute myocytolysis which was described by Dr. Howell and discussed at the last clinical pathologic conference of this type in 1960.[3]

PROF. ARNOTT: Yes! I had a sense of *déjà vu* there.

DR. HEATH: Well, I think that we may close the conference at that point, all agreeing that this is a case of rheumatoid aortitis with involvement of many of the peripheral arteries. There seems to have been an unusual agreement between clinicians and pathologists on this occasion!

Diagnosis: Rheumatoid aortitis

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Annotations

Atrial myxoma: a diagnostic challenge

During the past 6 years there have been increasingly frequent reports of the successful removal of an atrial myxoma from a critically ill patient, with pronounced improvement.[1,3,5,9] Hence, this tumor is no longer to be considered merely as a medical curiosity—a correct diagnosis has practical significance. A myxoma may masquerade as one of several entities: mitral stenosis, bacterial endocarditis, refractory congestive failure, pulmonary embolism, Adams-Stokes syndrome, and epilepsy. Therefore, the chief clinical problem lies in its proper recognition. In reviews of the case histories of patients with atrial myxomas, several diagnostic criteria have been underscored. These are: (1) syncope or severe dyspnea clearly related to change in posture; (2) variations in murmurs from one time of observation to another; (3) change in murmurs related to change in position; (4) unusually rapid deterioration despite careful medical treatment in a patient considered to have mitral stenosis; (5) the detection of myxomatous material in surgically removed emboli[3]; (6) absence of evidence on x-ray examination of chronic passive pulmonary congestion in a patient alleged to have severe mitral stenosis (or, when congestion is present, disparity in the degree of venous engorgement in the two lung fields[2]); (7) proportionately little increase in the size of the left atrium as determined by fluoroscopy in the presence of what appears to be "tight" mitral stenosis. Unfortunately, there have been several cases in which a myxoma was discovered, either at autopsy or at atriotomy for mitral valvuloplasty, when, despite a careful search, all of the aforementioned features proved to be absent.

Since the majority of myxomas are on the left side, the most frequent error encountered is the incorrect diagnosis of mitral obstruction by such a tumor as mitral stenosis of rheumatic origin. Periodically the medical literature contains accounts of the detection of an unsuspected myxoma during operation for mitral valvuloplasty. Unfortunately, a patient with a myxoma of the left atrium may lack all of the features described above and, instead, show the typical features of valvular disease of rheumatic origin, which include a history of rheumatic fever, loud first sound at the apex, a diastolic rumbling murmur with presystolic accentuation, a typical opening snap,[5,6] a history of hemoptysis, and evidences of pulmonary hypertension. Conversely, a patient with mitral stenosis of rheumatic origin is often found to have a variation in the intensity of the apical diastolic murmur from one examination to another, or with changes in position. The murmur of mitral stenosis may increase in intensity for several heart cycles after a change to any position, right lateral or upright as well as left lateral, presumably as the result of increased cardiac output during the effort of turning.[7] Finally, a filling defect in the left atrium on angiocardiography may represent atrial thrombus associated with valvular stenosis rather than a tumor mass.

It is apparent that, when characteristic features are absent, a myxoma may be indistinguishable from the typical mitral stenosis of rheumatic origin, and its discovery delayed until the surgeon inserts his finger into the atrium. Under these circumstances the prudent course for the surgeon would be to resist attempts to remove the mass until he can reopen the atrium under adequate hypothermia,[3,5] or under conditions of cardiopulmonary bypass,[1] preferably the latter. Attempts to remove the tumor mass under the usual surgical setting for mitral valvuloplasty have been unsuccessful, with a single exception.[8]

It is hoped that more definitive measures can be developed for the timely detection of intracardiac tumors. Angiocardiography has revealed tumor masses on several occasions and probably represents the most reliable diagnostic technique. However, there have been instances of both false positive[4] and false negative[9] diagnoses with this approach. Furthermore, the use of angiocardiography must relate to some clue sifted from clinical examination, unless one elects the rather unattractive course of performing it on all patients with apparent mitral stenosis.[4]

At the present level of diagnostic acuity, perhaps the most worth-while attitude for the clinician would be to withhold a diagnosis of mitral stenosis until he has made a conscientious search for all of the more unique features which may be produced by a myxoma. This amounts to asking in every case of mitral stenosis, "Could this patient possibly have a myxoma?" Given any of the features outlined above which are suggestive of an intracardiac tumor, one could justify angiocardiography and propose to the surgeon that an atriotomy be performed under cardiopulmonary bypass.

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The electrocardiogram in ventricular septal defect

During the past few years a great deal has been learned about the electrocardiogram in ventricular septal defect (VSD). The electrocardiogram formerly had been thought to be normal or at least of little diagnostic value in VSD. With the introduction of the concept of systolic and diastolic overloading by Cabrera and Monroy,[1] in 1952, and the subsequent extension of these concepts by Marsico and co-workers[2] and Sodi-Pallares[3] to VSD, a new diagnostic era was introduced. Several excellent articles have been published recently which describe the electrocardiographic features in large series of cases of VSD.[4-8] Of special interest has been the use of the electrocardiogram in evaluating the hemodynamics and in the selection of patients for corrective operation.[7,9-11]

Four basic electrocardiographic patterns occur in VSD: (1) normal; (2) left ventricular hypertrophy (LVH), usually of the diastolic overload type (DO); (3) right ventricular hypertrophy (RVH) of the systolic overload (SO) and/or diastolic overload (DO) types; and (4) combined ventricular hypertrophy (CVH).

A normal electrocardiogram has been found to occur in 10 to 15 per cent of the cases of VSD.[2,4,6,7] Pure or isolated LVH has been found in from 2 to 30 per cent of patients with VSD.[4,6,7] Left ventricular hypertrophy of the diastolic overload type (LVDO) is manifested in the left precordial leads (V_5, V_6) by tall R waves with delay in the onset of the intrinsicoid deflection, deep Q waves (2 mm. or >), and tall T waves.[1-3,9] It has been emphasized (especially in infants and children) that tall R waves accompanied by deep Q waves and tall T waves in Leads II, III, and aV_F indicate LVH (LVDO).[3,11] Deep S waves in the right precordial leads (V_1, V_{3R}) are also suggestive of LVH. The deep Q waves have been attributed to septal hypertrophy.[2,3,12] Occasionally, the left precordial leads will display inverted T waves (left ventricular systolic overloading).[8,12]

Right ventricular overloading has been found in from 14 to 65 per cent of the cases of VSD.[2,4,6,7] Right ventricular systolic overloading (RVSO) is manifested by dominant R waves (rR, R, Rs, qR) in the right precordial leads (V_{3R}, V_1) with upright (or inverted) T waves.[1-3] Right ventricular diastolic overloading (RVDO) is evidenced by the rSR′ pattern in the right chest leads.[1,3] Some workers have attributed this rSR′ configuration to hypertrophy of the crista supraventricularis, just as in atrial septal defect.[6]

Combined ventricular hypertrophy is encountered in from 20 to 61 per cent of the patients with VSD.[4,6,7] It can be diagnosed when the electrocardiogram displays the criteria for both RVH and LVH which have just been enumerated. When the right precordial leads display RVH, associated LVH may also be suspected if any of the following signs are present in the left chest leads: (1) R waves of normal amplitude when lower ones would have been expected; (2) prominent Q waves; (3) inversion of the T waves in V_6 when T waves are positive in right chest leads.[2,7]

The mean QRS axis in VSD has been found to range widely (occurring in any sextant), although the majority of cases vary from +30 to +150 degrees.[3,5-7,13] Cases with LVH tend to display a normal axis or left axis deviation (LAD), those with RVH tend to have right axis deviation (RAD), whereas those with CVH may exhibit LAD, RAD, or a normal axis.[7]

The terminal QRS forces tend to be rightward in the frontal plane in VSD. This gives rise in the standard leads to the S_1,S_2 or S_1,S_2,S_3 pattern in 70 to 90 per cent of the patients.[5,6]

The direction of the frontal plane QRS vector loop tends to follow the direction of the mean QRS axis.[7] Those cases with LAD tend to have counterclockwise rotation of the loop, and those with RAD to have clockwise rotation, although exceptions occur.[5,7] DuShane and Kirklin[11] have found that a counterclockwise QRS loop in the frontal plane with a QRS axis ranging from +60 to −60 degrees is usually indicative of left ventricular overloading in infants. Toscano-Barboza and DuShane[5] found that 15 per cent of their cases of VSD displayed counterclockwise rotation of the QRS loop above

the isoelectric line (or a figure-of-eight along this horizontal line) similar to that found in patients with atrioventricular cushion defects.[14] This same electrocardiographic pattern has been described recently by Neufeld and associates[15] as being found uniformly in what they term *isolated VSD of the persistent common atrioventricular canal type.*

Katz and Wachtel[16] have described large diphasic QRS complexes in congenital heart disease. This pattern has been encountered (in the limb and/or mid-precordial leads) in from 10 to 72 per cent of the cases of VSD[2,5,6,8,17,18] and has been thought to suggest CVH.[18]

P waves which suggest left atrial enlargement have been found in from 2 to 33 per cent of the cases.[2,4-7] Evidence of right atrial enlargement has been found in from 10 to 25 per cent of the cases.[2,4-6] Atrial fibrillation is uncommon in VSD.[5,6] Complete right bundle branch block occurs in a few cases.[7,19]

Interesting observations have been made concerning the change in the form of the basic electrocardiographic patterns that infants and children with VSD will display when followed for several years.[4,7] The majority show no change in their patterns. A moderate number of infants with normal patterns or RVH will show increasing evidence of LVDO. This has been interpreted as a normal regression of the increased pulmonary vascular resistance of infancy with resulting increased pulmonary blood flow and is a favorable sign.[7] Only rarely was pure RVH noted to develop during the period of observation.[4,7]

The correlation of the hemodynamic and electrocardiographic findings and the role of the electrocardiogram in the selection of cases of VSD for corrective operation has been especially stimulating and rewarding.[7,10,11]

Those patients with small defects, small left-to-right shunts, low pulmonary blood flow, and no pulmonary hypertension have a normal electrocardiogram without ventricular hypertrophy.[6,7,19,20]

Those patients who have larger defects, moderate to large left-to-right shunts, and increased pulmonary blood flow have an increased load on the left ventricle, and the electrocardiogram displays LVDO.[7,10,11] Such patients usually are good candidates for surgical repair of the VSD.[7,11]

A large portion of patients with VSD have pulmonary hypertension, either hyperkinetic (due to a large pulmonary flow) or due to increased pulmonary vascular resistance (secondary to organic change in the pulmonary vascular bed), or both.[11,21,22] The pulmonary hypertension will produce RVH, whereas the increased pulmonary blood flow and increased return to the left ventricle will produce LVH, so that the electrocardiographic pattern will be one of CVH.[7,11] However, as long as the electrocardiogram displays good evidence of LVDO, there is still usually an increased pulmonary blood flow, and the patient will benefit from operation.[7,11]

When the electrocardiogram shows pure RVH (SO), the pulmonary vascular resistance and pulmonary blood pressure are usually quite high and the pulmonary blood flow is decreased (less than systemic blood flow).[7,11] Although there are exceptions, surgical repair of the VSD of the patient with this electrocardiographic pattern is usually contraindicated.[7,11]

Not all workers have found such good correlation between the electrocardiographic patterns and hemodynamic changes in VSD.[8] In fact, even among those who have found good electrocardiographic-hemodynamic correlation, there is lack of agreement on the precise electrocardiographic criteria that should be used in the selection of patients for operation.[7,11]

It should be emphasized that associated anomalies may affect the electrocardiographic pattern in VSD. Although RVH usually indicates pulmonary hypertension, it should also raise the possibility of pulmonic or infundibular stenosis.[4] Electrocardiographic evidence of LVH ordinarily indicates a dominant left-to-right shunt in VSD, but it should be recalled that associated mitral insufficiency, aortic stenosis, or aortic insufficiency may also produce LVH.[11,23,24]

In summary, it may be stated that the electrocardiogram is an extremely valuable tool in the clinical and preoperative evaluation of patients with VSD. However, it must be emphasized that the electrocardiogram is only one aid, and a thorough evaluation of the patient must include a careful history, physical examination, cardiac x-ray examination, and fluoroscopy, and, in selected patients, cardiac catheterization.[4,10,11,20]

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Proposed design for mechanical ECG screening technique

Automatic, mechanical screening or interpretation of electrocardiographic records is a task which has recently captured the interest of various investigators. Although the task appears feasible to some, particularly engineers, physicians who are familiar with the problem tend to regard it as not feasible. At least two research projects are known to be underway (Airborne Instruments Laboratory in cooperation with the Sloane-Kettering Institute, and the Veterans Administration in cooperation with the National Bureau of Standards), both of which are seeking to develop ways of reducing the interpretation of electrocardiograms to digital computer analysis. The National Institutes of Health recently undertook a preliminary study of a similar approach, but has abandoned it (October, 1960). A reliable and practical method has not yet been reported from any source (July, 1960, review of the literature). Cardiologists tend to share with physicians in general a distrust of any mechanical or subprofessional procedure which arrives at diagnostic decisions. Their viewpoint is well founded, since it is based on a knowledge of the ways in which clinical measurements often show an overlap among normal variations, pathologic states, and technical errors. They often insist that the clinical judgment of a physician is needed to make the proper differentiation.

A major impetus which stimulates the search for mechanical methods of interpreting ECG records is the occasional need for screening very large numbers of people. For example, since July, 1959, the Federal Aviation Agency has established a requirement that all pilots of commercial airlines undergo serial ECG examinations. All pilots are required to have a base-line record at age 35, and annually after the age of 40. During the first 6 months this rule was in effect a total of 13,000 electrocardiographic records had been received, and about 8,000 had been reviewed.[1] The number of ECG records to

be reviewed by the Federal Aviation Agency is expected to reach a total of 50,000 annually. The Armed Forces also have a large-scale screening problem with both flying personnel and officers in the over-40 age group. The United States Air Force recently reported a survey of 67,000 ECG records[2]; the Canadian Air Force has reported a survey of a group of 17,000.[3] Various public health projects have also undertaken the large-scale ECG screening of certain populations.

The manpower problem involved in making extensive ECG surveys of large populations becomes nearly prohibitive. Not only is the scarcity and high cost of cardiologists an obstacle, but the sheer monotony of large surveys is a deterrent to the recruitment of personnel as well as a threat to the accuracy of interpretation. Mechanical methods for improving the efficiency of utilization of a cardiologist's time appear to be much more feasible at the present time than do methods for achieving a complete mechanical substitute for the cardiologist.

One possible way of achieving a considerable improvement in the utilization of the time of the cardiologist appears to be immediately feasible. A type of ECG pattern exists which, for the purpose of the discussion, is termed *clearly normal*, and which is highly uniform for a large proportion of normal people. In a large population of presumably healthy people (such as military personnel and commercial pilots) a major portion of the total will be found to be normal, of which a large majority will be *clearly normal*. In the large surveys mentioned above, for example, it was found that 91.3 per cent of the airline pilots, 96 per cent of the United States Air Force pilots, and 94 per cent of the Royal Canadian Air Force pilots had normal ECG records. A mechanical means for identifying and sorting out the *clearly normal* records in a large sample would make it possible to eliminate 80 to 90 per cent of the tasks of the cardiologist, and thus allow him to confine his attention to the abnormal records and normal variations.

Suggested plan for design of a fail-safe device for sorting normal electrocardiograms. A relatively well-standardized method developed in one of the nonmedical fields appears to be applicable to this problem. The people in the missile guidance program have developed a method for determining, automatically, whether a radar representation of a certain piece of terrain conforms to aerial photos of the area.[4] This map-matching technique can be applied to the matching of ECG records with normal standards. A suggested plan for designing a device which will automatically sort out normal ECG records follows:

1. The first step would be to develop a Master Normal ECG Profile, within the limits of which a large percentage (the *clearly normal*) of normal ECG records fall. Standards for clearly normal records are sufficiently well defined to render it feasible to establish a two-dimensional profile in the form of a photographic (positive) transparency. The specifications for this master would be such that a substantially large percentage of normal ECG records fall, profile-wise, within its limits, and portions of all other records fall outside its limits.

2. The second step would be to apply the map-matching technique for the purpose of making optical comparisons between the master profile and sample ECG records. Application of this technique to ECG screening would consist of matching the photo-positive master profile with a photo-negative of the sample record. An exact positional match of the two photographs would block the passage of a beam of parallel light produced by an optical system. When the master profile completely blocked the passage of light through the sample record, a clearly normal ECG record would thereby be identified. Any ECG record of which the profile is different from the master profile, or any record with technical imperfections, will permit light to pass through the optical system and to activate a photoelectric sensor. The signal resulting from the sensor would then act to separate such a record from those which are clearly normal.

3. The next step would be to prepare the preliminary specifications for an automatic machine to perform the optical matching process. The degree to which it is necessary to normalize the records for amplitude and period would be determined. If it is necessary, normalization would be accomplished with the use of a cylindrical lens, or by mechanically moving the master profile about either its longitudinal or vertical axis. The fail-safe principle can be incorporated in the process, according to which all imperfections, all artifacts, as well as all records not clearly normal would be sorted out from the clearly normal records. Those not clearly normal would be subjected, subsequently, to the conventional method of individual examination by a cardiologist.

4. A manual machine could be constructed as a model for the purpose of testing the reliability of the proposed screening method and for making suitable refinements in the design of the system. In particular, the model would be useful in making improvements in the master normal profile. When the feasibility of the method has been determined from the manual machine, an equipment manufacturer might be included in subsequent plans for the construction of an automatic machine. Finally, determinations would be made on the number of leads and the number of cardiac cycles which would be required in order to obtain reliable results.

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Polypeptides, proteins, man, and nature

Within recent years a new field in biochemistry which involves amino-acid and polypeptide chemistry has unfolded. The newly synthesized polypeptides have existed in living organisms for millions of years, but man is just beginning to discover those which occur naturally and to synthesize new ones. These amino-acid complexes are potent, being active in microgram quantities. Among these are oxytocin,[1] vasopressin,[2] angiotensin II,[3,4] bradykinin,[5] and others.[6] Many more are to evolve in response to the fancies of those chemists who do research on the proteins and polypeptides, and the physiologist is destined to enjoy investigating their many specific and interesting actions.

Not only are physiologically potent polypeptide complexes many, but so are amino-acid complexes: for example, tyrosine, adrenaline, noradrenaline, isopropyl arterenol noradrenaline, 5-hydroxytryptamine, heparin, histamine, and others. The single modified amino-acid and the multiple amino-acid units are necessary components of the regulatory life processes of many organisms, including man. Most, if not all, of those listed above are extremely potent regulators of cardiovascular function. Many are yet to be discovered.

The proteins of the body are much like the water of the body, and nature is the efficient, economical, and "wise" organizer and operator of the life processes. Because water, that wonderful substance, is ever present in great abundance in all sites in the body, it is "wise" to use it as much as possible for as many processes as possible. And so it is used. Its functions are many; it transports heat, lubricates, splits or hydrolyzes fats, carbohydrates, and proteins in most metabolic processes, provides hydrogen for hydrogen bonds, and acts as a dielectric. It is the great transportation vehicle of cells and metabolic substances (food, oxygen, and wastes). It cools the body, insulates thermally as well as electrically, and buffers the body against sudden physical and chemical changes. It is plentiful and necessary for life and is made to serve many necessary life functions.

So it appears for proteins. They are ever present in abundance at every site in the body. The amino acids are the chemical and physiologic alphabet of living organisms, the dots and dashes of the physiologic Morse code. When the amino acids and their order in the polypeptide chain are varied, specific functional symbols of specific physiologic responses follow. One chain of amino acids (oxytocin) in specific order (as letters in language or dots and dashes in wireless communication) causes the uterus to contract; another (angiotensin II) causes the arterioles to contract, and still another (bradykinin) causes the arteriovenous shunts of the digits and skin to constrict,[7] and so forth. That *nature* should make so many important uses of a single substance, protein, and its amino-acid components in a highly temporally organized living being, such as man, should be expected. In the development of living things from the original fundamental energy of the universe, nature should be expected to make as much use as possible of what is lying about to keep the organization simple and to meet readily the needs of the temporally dependent life processes.

It is also interesting to note that, in the development of this system, specific amino-acid complexes, proteins, are also used as catalysts in the synthesis and digestion of other amino-acid complexes, proteins and polypeptides, a truly efficient, economical, and dependable design. Many important parts of cells and organ systems are constructed of proteins which perform interesting functions, such as contraction of muscle.

One can readily extend these thoughts further, not only for water and proteins but for other substances and complexes thereof. It is exciting to see the new amino-acid alphabet of biochemistry and physiology, and it is important to note it in this JOURNAL which is devoted to studies of the cardiovascular system.

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Book reviews

AN ATLAS OF ACQUIRED DISEASES OF THE HEART AND GREAT VESSELS. By Jesse E. Edwards, M.D., Consultant, Section of Pathologic Anatomy, Mayo Clinic, and Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn. With the counsel and collaboration of H. N. Neufeld, R. D. Pruitt, R. L. Parker, and H. B. Burchell. Philadelphia, 1961, W. B. Saunders Company, 1401 pages plus index. Price of 3-volume set: $70.

This work is comprised of 3 volumes, as follows: Volume I—Diseases of the Valves and Pericardium (pp. 1-484 plus index). Volume II—Coronary Arterial Disease, Systemic Hypertension, Myocardiopathies, the Heart in Systemic Disease, and Cor Pulmonale, Acute and Chronic (pp. 485-984 plus index). Volume III—Diseases of the Great Vessels (pp. 985-1401 plus index).

The essence of this work lies in the correlation of functional with structural aspects of acquired cardiovascular disease. Clinical and laboratory manifestations of disease are presented and then related to their pathologic anatomic counterparts.

The material is based on data drawn from case histories of hundreds of patients admitted to the Mayo Clinic over the last 14 years. The presentation is largely pictorial in nature, with discussion frequently in short case-report form. In general, the illustrations are excellent. There are over 4,000 reproductions, including pertinent electrocardiograms, roentgenograms, pressure curves, diagrams, photographs, and photomicrographs. The text is well written but quite brief.

The cardiologist may find the clinical discussions too superficial, but both he and the cardiovascular surgeon could gain much from the pathologic orientation of these presentations. The price may discourage inclusion of these volumes in personal libraries, but all those involved in the study of diseases of the cardiovascular system should be aware of their availability as a reference work. The work is probably best suited for libraries with liberal budgets.

Doctor Edwards is an outstanding and leading authority in the field of cardiovascular pathology. These volumes will contribute to the dissemination of knowledge concerning basic clinical and pathologic interrelationships.

SYMPOSIUM ON ANTICOAGULANT THERAPY. Report of the Proceedings of a Symposium held at the Royal Society of Medicine, Nov. 18 and 19, 1960. Edited by Professor Sir G. W. Pickering, M.A., D.Sc., M.D., F.R.C.P. (Lond.), Regius Professor of Medicine, University of Oxford. London, Harvey & Blythe, Ltd., 284 pages. Price: 21 s.

This is a report of the proceedings, in book form, of a symposium on anticoagulant therapy held at the Royal Society of Medicine, England, November, 1960. Each of eight sessions, with the panel discussions, are published as separate chapters. A total of 54 individuals participated in the symposium; 19 of these presented papers, and the others entered into the panel discussions. Although the majority are from Great Britain and the United Kingdom, important contributions are made by Nicola, of Italy, Koller, of Switzerland, Owren, of Norway, and Millikan, of the United States.

Only brief discussion is made of the known and theoretical action of anticoagulants on coagulation mechanisms and the specific biochemical changes effected by therapy. The discussions, for the most part, are related to the practical experiences in the use of anticoagulants in a variety of cardiovascular abnormalities, and to the methods of controlling the therapy and dosage necessary to provide maximum benefit consistent with safety. Difficulty is experienced in attempting to relate some of these experiences to American medicine because of the differences in methods of practice. Considerable discussion is given to the role of clinical pathologists, the general practitioner, and the consultant in the management of the patients in large clinics, especially in prescribing dosage of drugs.

All admitted that, in view of a rapidly increasing number of patients who are receiving therapy, there is a great need for a simple, inexpensive, reliable testing procedure sensitive to the multiple factors responsible for thrombogenesis and bleeding. While some gave strong support for, and pointed out the advantages of, the recently developed "Thrombotest" of Owren, the majority considered the one-stage prothrombin test of Quick, which is the most widely used procedure, to be the most reliable. Problems with this test, such as its poor sensitivity to some coagulation factors, the variable activity of brain thromboplastins, and the existing confusion in the reporting and interpreting of results are discussed at length. Advantages and disadvantages of testing capillary blood versus venous blood are discussed.

Impressive statistics for the benefits of long-term therapy in coronary disease are presented by Suzman, of Johannesburg, and Wood, of London, for short-term therapy in the prevention of troublesome venous thrombus and pulmonary embolism in the injured patient by Sevitt, of Birmingham, and for long-term therapy of intermittent insufficiency in the carotid and vertebral-basilar system by Millikan, of the United States. Fewer claims and less enthusiasm are given for therapy in peripheral vascular disease, pulmonary hypertension, and mitral valve disease, and conflicting opinions and experiences are given for therapy of acute cerebral thrombosis.

The panel discussions, in general, are excellent. Differences of opinion and experiences are handled with due consideration and respect, but discussed frankly, with a good sprinkling of British humor.

This report contains much practical informa-

tion and should be helpful to all physicians who are actively concerned with anticoagulant therapy.

MODERN TRENDS IN CARDIOLOGY. Edited by A. Morgan-Jones, M.Sc., M.B., F.R.C.P., Director, University Department of Cardiology, Manchester Royal Infirmary; Reader in Cardiology, University of Manchester; Consultant Physician, United Manchester Hospitals. New York, 1961, Paul B. Hoeber, Inc., 264 pages. Price $14.50.

With the welter of recently published books and monographs on cardiovascular physiology and disease, one might wonder how another volume treating of this subject could be produced without trite reiteration. Nevertheless, this volume, skillfully edited by Morgan-Jones, presents selected discussions of various facets of cardiovascular physiology in a sufficiently different light to bring them into new focus. The volume is made up of sixteen chapters by British, American, Canadian, and Swedish physicians who are acknowledged experts in their special fields. Each of the chapters has been written in terms of current ideas and the shaping of problems in the selected fields, some of which border upon cardiovascular disease where their importance to circulatory physiology has become apparent. The technical aspects of investigative problems receive lesser emphasis. The net result is a most interesting collection of essays that describe, and clarify, various physiologic processes of interest.

The book opens with a chapter by Bing on cardiac muscle metabolism. It continues in succeeding chapters with discussions of the circulatory dynamics of the left heart; pulmonary function in heart disease, and pulmonary vascular resistance (presented with admirable lucidity); renal function, electrolyte metabolism, metabolic factors in the etiology of coronary disease, congestive heart failure, and certain therapeutic aspects of cardiovascular disease.

This little volume should serve as a reservoir of valuable adjunctive information for students, teachers of medicine, and physicians who wish to broaden their grasp of many of the present trends in cardiovascular investigation, and currently important concepts of cardiovascular disease.

Announcement

On January 27, 1962, at the Mayo Memorial Auditorium of the University of Minnesota a scientific program will be presented in honor of the eightieth birthday of Dr. George E. Fahr, Professor Emeritus of Medicine. Papers will be read by his former students, and in the evening at a dinner at the Minneapolis Club his portrait will be presented to the Medical School. Dr. Howard B. Sprague, past President of the American Heart Association, will be the speaker. His topic will be: "Dr. George E. Fahr and His Era."

For further information, call or write Arthur C. Kerkhof, M.D., Medical Arts Building, Minneapolis 2, Minnesota.

American Heart Journal

An international publication for the study of the circulation

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JULY-DECEMBER, 1961

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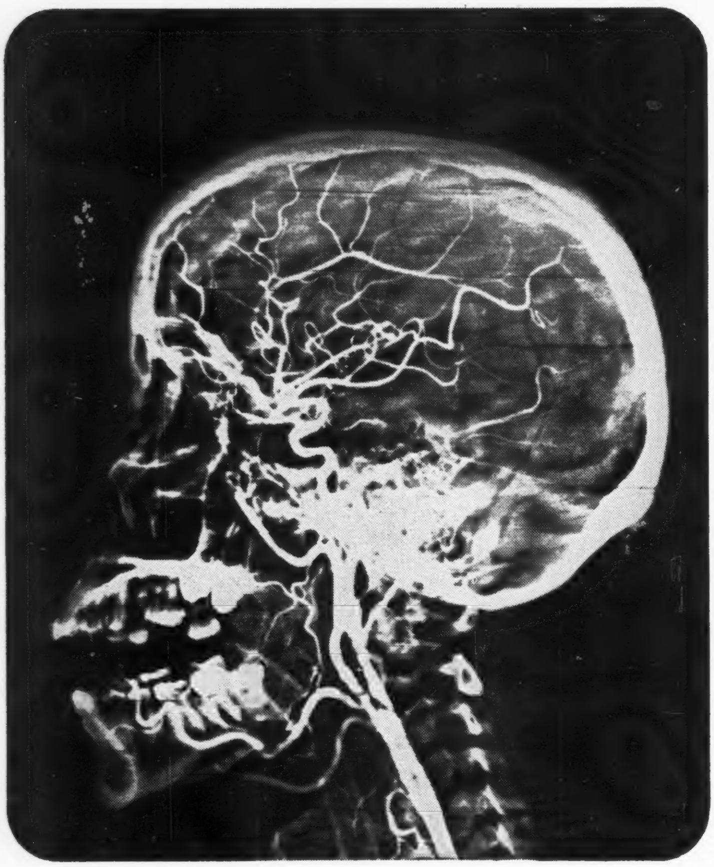

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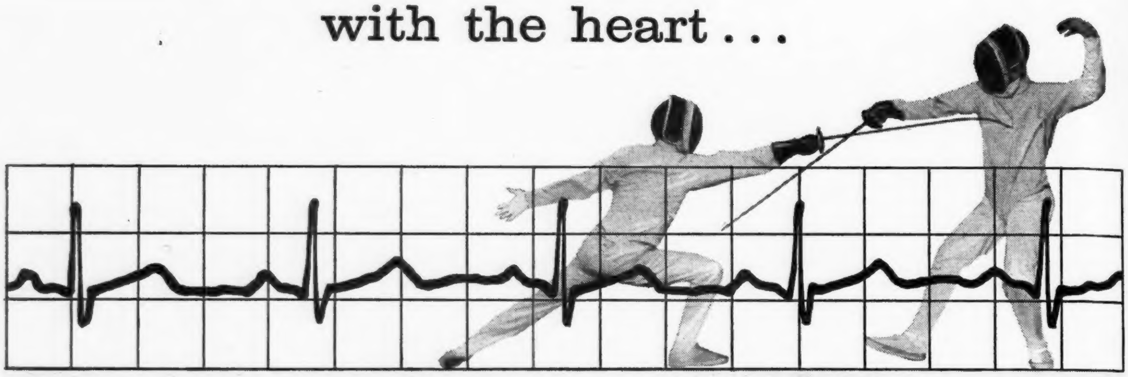

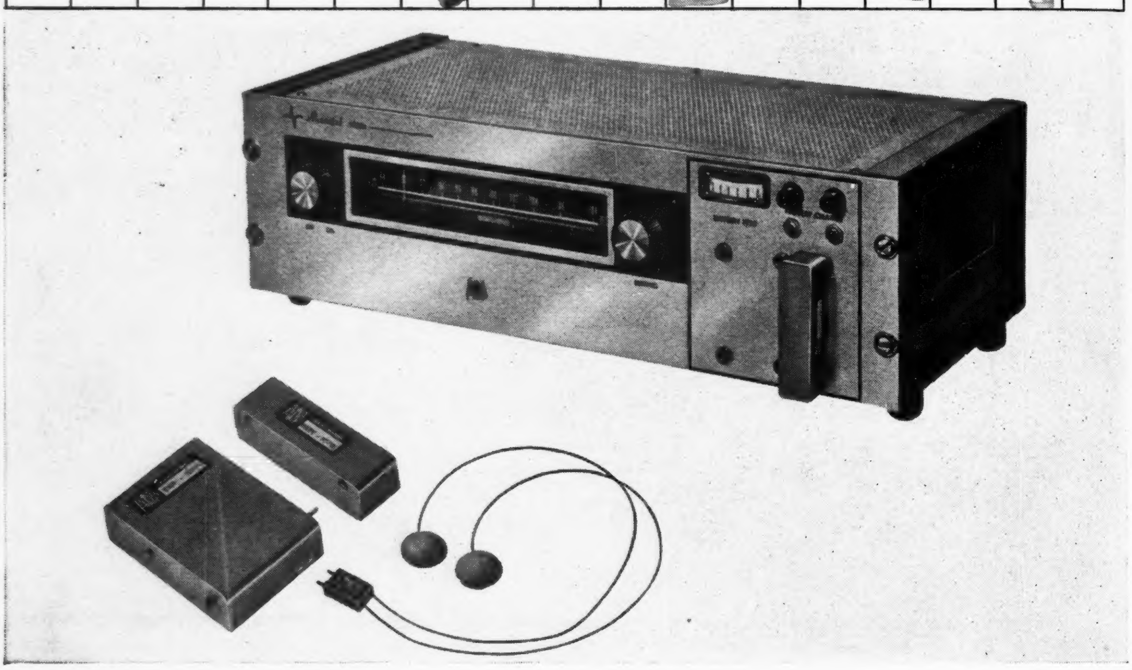

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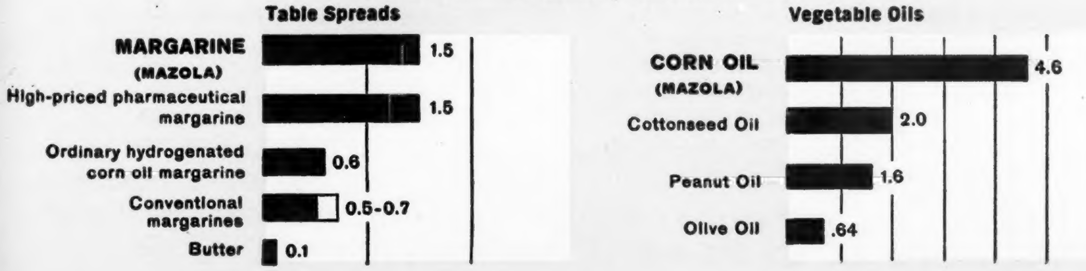

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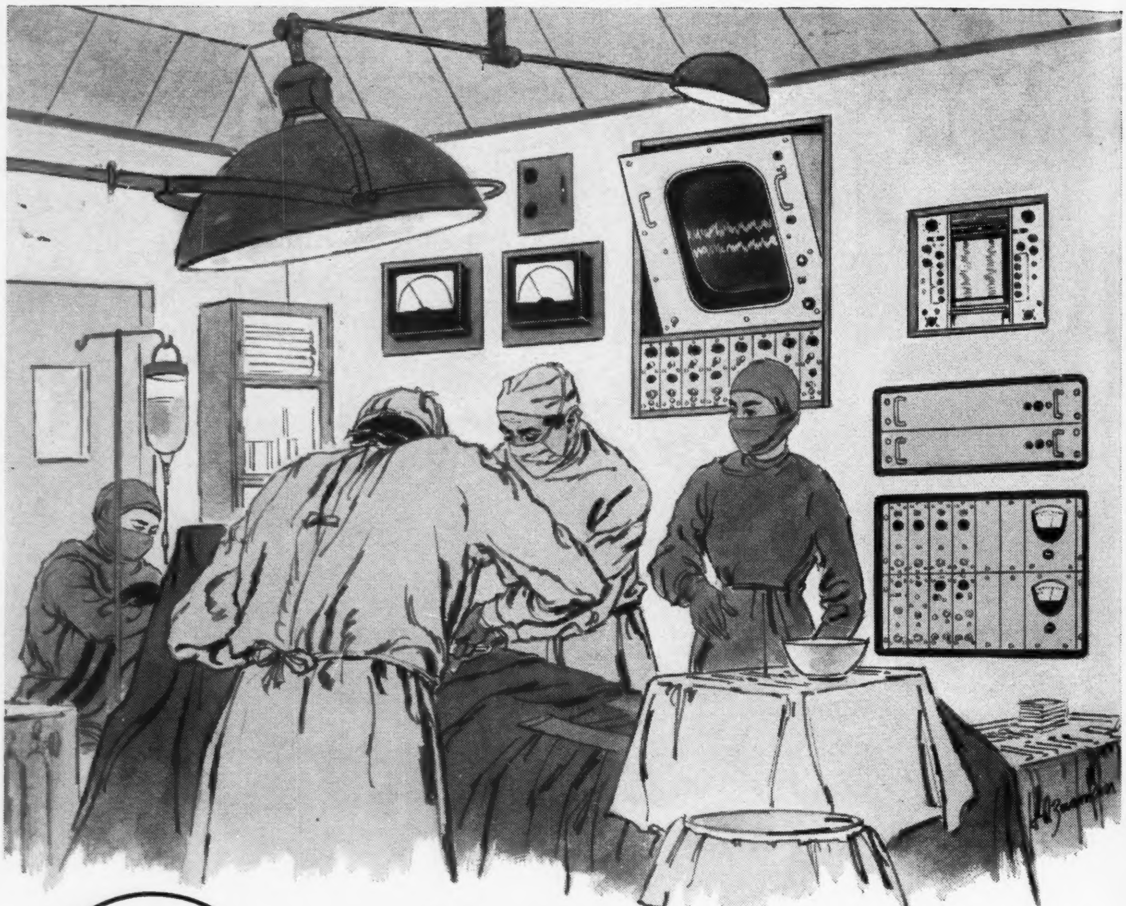

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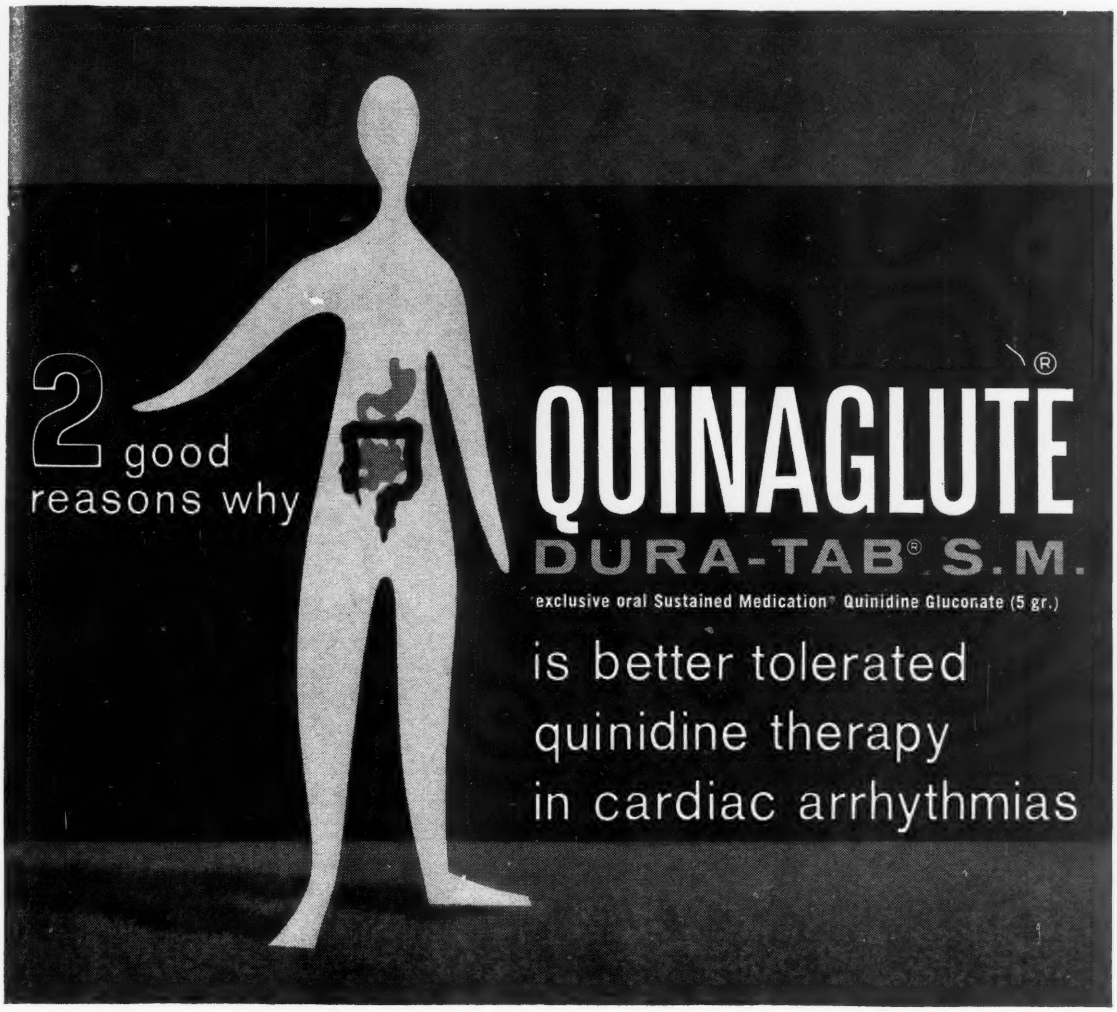

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PENTRITOL—Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown excellent results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity of physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol-B Tempules, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

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in short- or long-term anticoagulant therapy

prompt, predictable, reproducible results • "leads to an initial rapid fall in prothrombin activity...."[1] Therapeutic levels attained in 48 to 72 hours • achieves "a rather uniform and predictable fall in prothrombin activity."[2] • "Results are reproducible."[3]

easy reversibility...and prompt restoration of effect • vitamin K_1 "counteracted the effect of MIRADON in a predictable fashion in 5 to 8 hours."[4] • "The anticoagulant effect can be restored rapidly by remedication."[1]

"even-keel" stability in maintenance therapy • "Once the prothrombin levels had been reduced to the therapeutic bracket, they were maintained there with little difficulty on daily doses of the drug...."[5]

Packaging: MIRADON Tablets, 50 mg., bottles of 100. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

References: (1) Lange, K., *et al.:* Am. Heart J. *55*:73, 1958. (2) Lange, K., *et al.:* Anisindione: A new improved anticoagulant, Scientific Exhibit, 106th Ann. Meet., A.M.A., New York, June 3-7, 1957. (3) Blaustein, A.: New York J. Med. *58*:701, 1958. (4) Connell, W. F., and Mayer, G. A.: Canad. M.A.J. *80*:785, 1959. (5) Paul, H. A., *et al:* Surg. Gynec. & Obst. *108*:605, 1959.

S-821

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We pharmaceutical manufacturers, over the past several years and in various ways, have been trying to tell the story of the drug industry's role as a member of the American health team, and thus to correct certain unfortunate misconceptions. And all along we have looked upon you of the medical profession, on whose good will we are so dependent, as perhaps our chief audience.

But now we wonder . . . because so many of you have said to us lately, either orally or in writing, "Why are you telling us this? Our patients are the ones who really need to hear this story."

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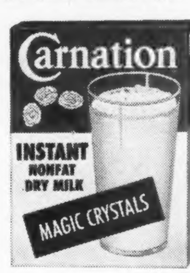
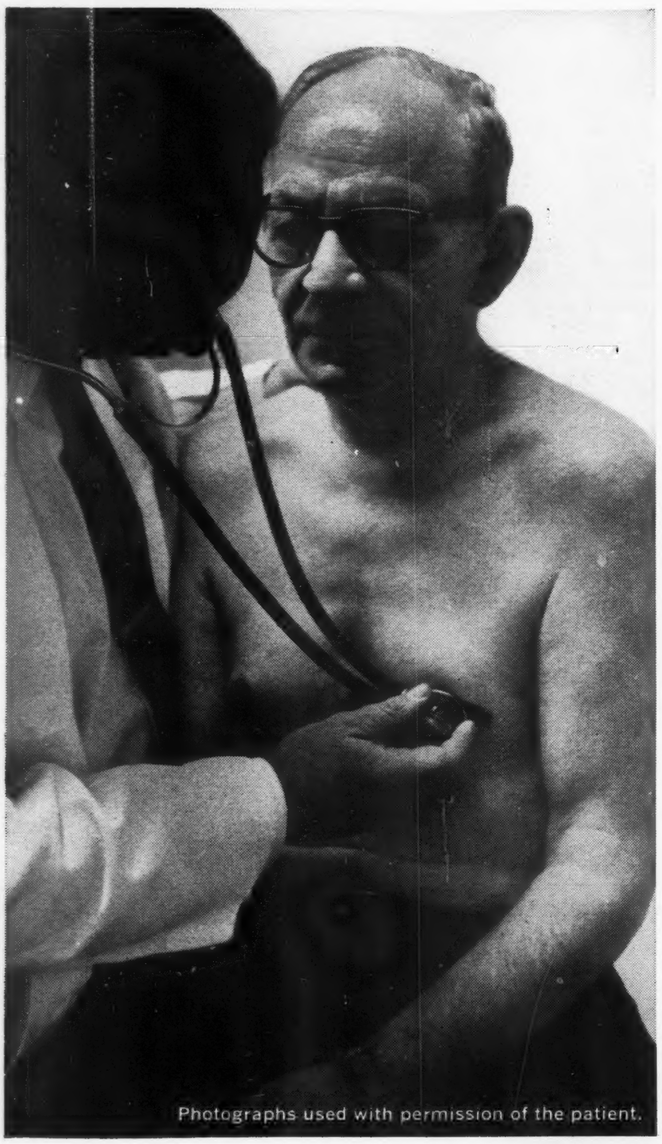


ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

Hypertension and congestive failure controlled with Serpasil®-Esidrix®



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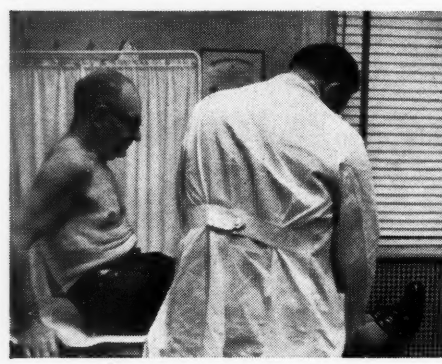
Mr. H.V., a 61-year-old retired pharmacist with hypertensive arteriosclerotic heart disease, was hospitalized in 1957 after a myocardial infarction. Blood pressure at this time ranged from 176/100 to 184/106 mm. Hg. The patient had associated congestive failure with ankle edema and dyspnea.

Serpasil-Esidrix Tablets #1 were added to the existing regimen of digitalis and low-salt diet in April, 1959. In the first 6 weeks of treatment, blood pressure decreased steadily to a range of 156/80 to 166/84 mm. Hg. Examination at the end of 6 weeks revealed no evidence of congestive failure. Neck veins were no longer distended; ankle edema was not present.

Mr. V.'s blood pressure is now stabilized at a satisfactory level and he has had no side effects from Serpasil-Esidrix. He can climb stairs without shortness of breath; he gets around more easily and feels better generally.



Serpasil-Esidrix combines in one tablet the antihypertensive and calming effects of Serpasil with the diuretic and anti-hypertensive-potentiating actions of Esidrix—for control of high blood pressure plus many complications.

SUPPLIED: **Tablets #2** (light orange), each containing 0.1 mg. Serpasil and 50 mg. Esidrix; bottles of 100. **Tablets #1** (light orange), each containing 0.1 mg. Serpasil and 25 mg. Esidrix; bottles of 100.

SERPASIL® (reserpine CIBA)
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For complete information about Serpasil-Esidrix (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N.J. 2/2960MB

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Serpasil®-Esidrix®
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she wakes refreshed

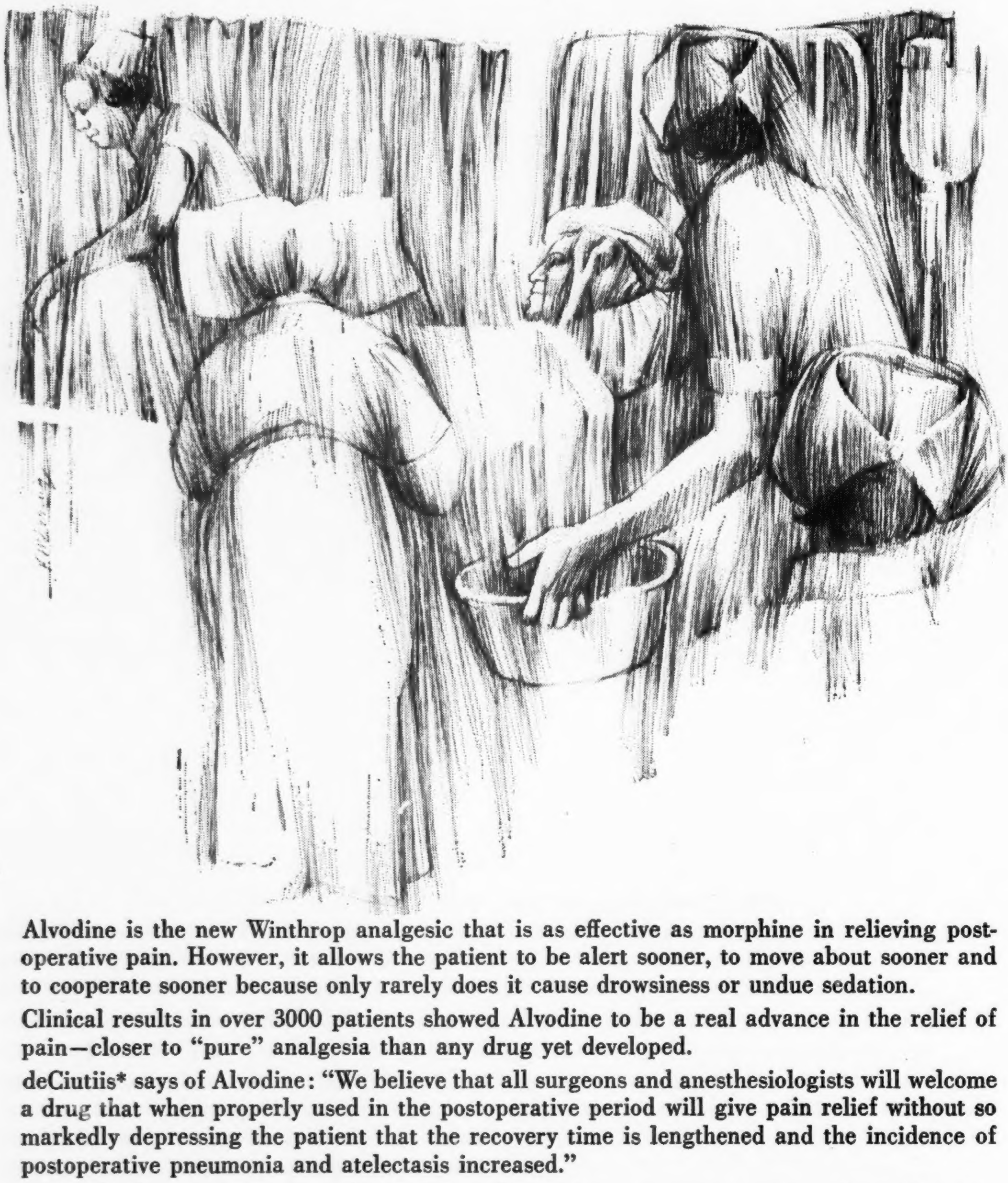
morning dose controls blood pressure all day

her food tastes better (thanks to salt liberalization)

edema relieved (shopping easier)

"cardiac fears" allayed (zest for life returns)

THEN—postoperative analgesia meant lengthy immobilization with more complications and slower recovery.



Alvodine is the new Winthrop analgesic that is as effective as morphine in relieving postoperative pain. However, it allows the patient to be alert sooner, to move about sooner and to cooperate sooner because only rarely does it cause drowsiness or undue sedation.

Clinical results in over 3000 patients showed Alvodine to be a real advance in the relief of pain—closer to "pure" analgesia than any drug yet developed.

deCiutiis* says of Alvodine: "We believe that all surgeons and anesthesiologists will welcome a drug that when properly used in the postoperative period will give pain relief without so markedly depressing the patient that the recovery time is lengthened and the incidence of postoperative pneumonia and atelectasis increased."

With Alvodine, respiratory and circulatory depression are rare; nausea and vomiting are uncommon. Alvodine does not cause constipation.

Alvodine ampuls of 1 cc. contain 20 mg. Usual adult dose: from 0.5 to 1 cc. by subcutaneous or intramuscular injection every four hours as needed. Also available in scored tablets of 50 mg. for oral administration. *Narcotic blank required.*

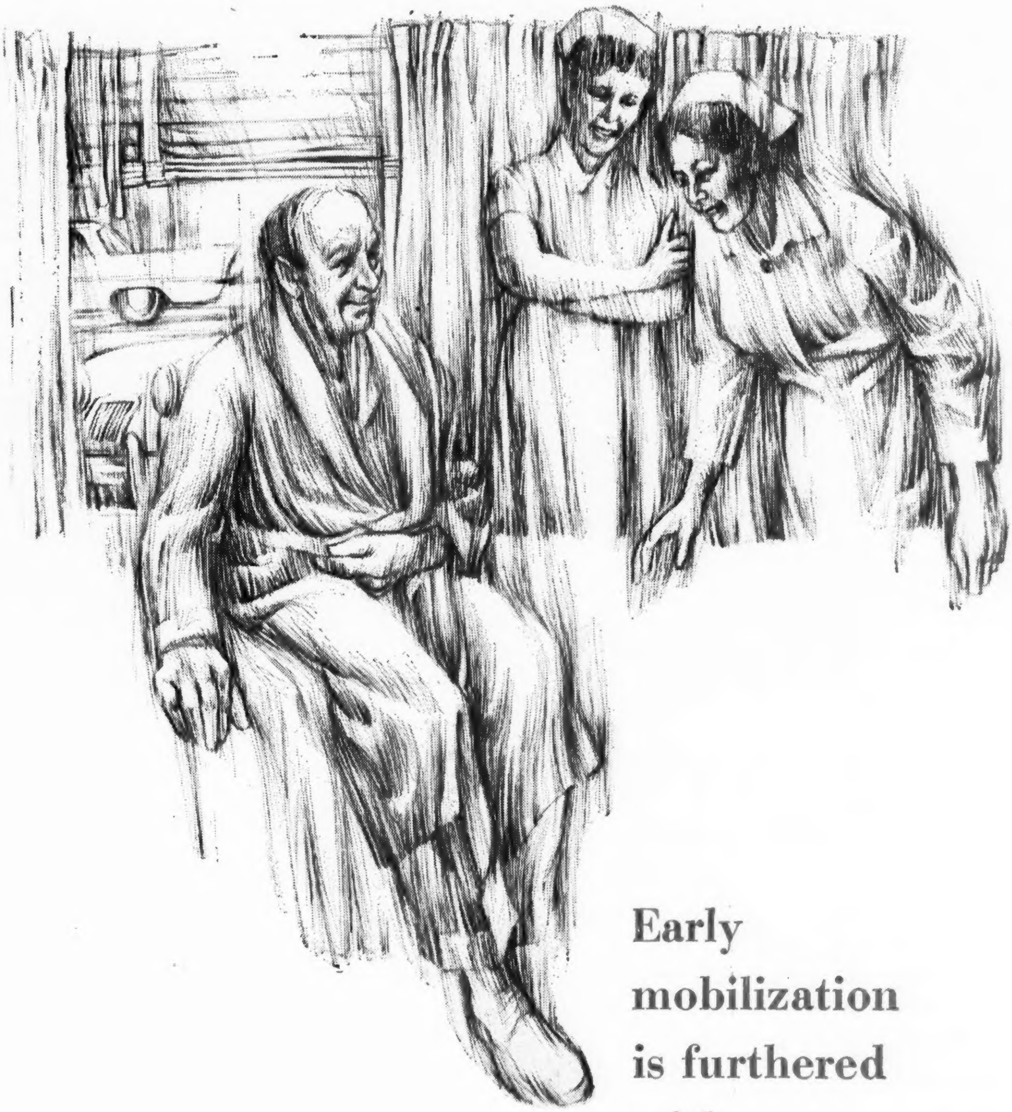
*deCiutiis, V. L.: Evaluation of Alvodine: a new narcotic analgesic, a double blind study, *Current Res. Anesth. & Analg.* 40:174, March-April, 1961.

Alvodine (brand of piminodine ethanesulfonate), trademark reg. U.S. Pat. Off.

Before prescribing be sure to consult Winthrop's literature for additional information about dosage, possible side effects and contraindications.

Winthrop
LABORATORIES
New York 18, N.Y.

NOW—postoperative analgesia usually means early mobilization, faster recovery and fewer complications.



Early mobilization is furthered with

New Alvodine®

Brand of piminodine ethanesulfonate *ethanesulfonate*

postoperative analgesia and alertness

Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

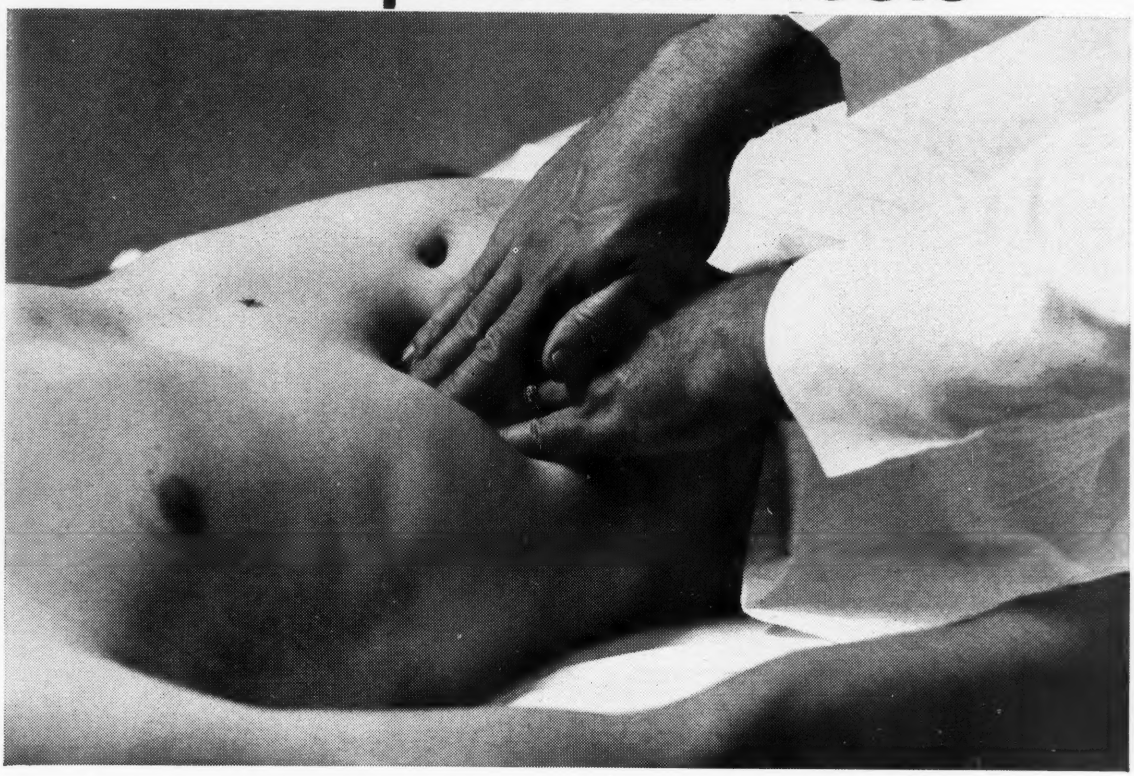
CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

in hepatic cirrhosis



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may prolong life...restore patients to productive capacity

Aldactone, which has demonstrated its ability to relieve resistant cardiac edema and ascites, has been found particularly effective in relieving the edema of hepatic cirrhosis.

The consistently high level of urinary aldosterone and aldosterone secretion rates in cirrhotic patients indicate that excessive production of this potent salt-retaining hormone is a major factor in their retention of fluid. As a selective aldosterone blocker, Aldactone may be relied on to relieve aldosterone-induced edema and ascites.

Clowdus and his co-workers[1] gave Aldactone to eight cirrhotic patients whose condition had failed to respond to salt restriction and conventional diuretics used singly and in combination. All responded satisfactorily when Aldactone was added to their therapeutic regimen.

In summarizing their experience with Aldactone these investigators state: "Aldactone, in conjunction with other diuretics and dietary sodium restriction, produced a striking and sustained diuresis in each of eight patients with ascites that had previously been refractory to treatment."

Indications: Edema and ascites associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome and idiopathic edema.

Dosage and Supply: To take advantage of a highly useful synergism and to secure immediate optimal diuresis, Aldactone should ordinarily be administered with a full dosage of a thiazide diuretic. The recommended adult dosage of Aldactone, alone or in combination, is 100 mg. four times daily. As much as 1,200 mg. may be given daily but will rarely be necessary. Aldactone should be administered cautiously to patients with hyponatremia or hyperkalemia, and potassium supplementation should not be used. Aldactone is supplied as compression-coated yellow tablets of 100 mg.

1. Clowdus, B. F.; Higgins, J. A.; Rosevear, J. W., and Summerskill, W. H. J.: Treatment of "Refractory" Ascites with a New Aldosterone Antagonist in Patients with Cirrhosis, Proc. Staff Meet. Mayo Clin. 35:97 (March 2) 1960.

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References: 1. Zapata-Diaz, [illegible] 2. Modell, W., in Drugs of Choice, [illegible] p. 419. 3. Kayden, H. [illegible] 1951. 4. Miller, H., et al.: J.A.M.A. [illegible]

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organic changes
edema
restricted salt intake

THE DIFFERENCE

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- a "wide range" antihypertensive
- effective by itself in a majority of patients with mild or moderate hypertension, and even in many with severe hypertension
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250 mg. DIURIL chlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to four times a day.*

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500 mg. DIURIL chlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to three times a day.*

*It is essential to reduce the dosage of other antihypertensive agents, particularly the ganglion-blockers, by at least 50 per cent immediately upon addition of these agents or of Diupres Tablets to the regimen.

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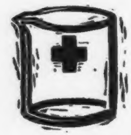

2. Safety verified by toxicity tests.

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Raudixin

Squibb Standardized Whole Root Rauwolfia Serpentina

Supply: 50 and 100 mg. tablets. 'Raudixin'® is a Squibb trademark.

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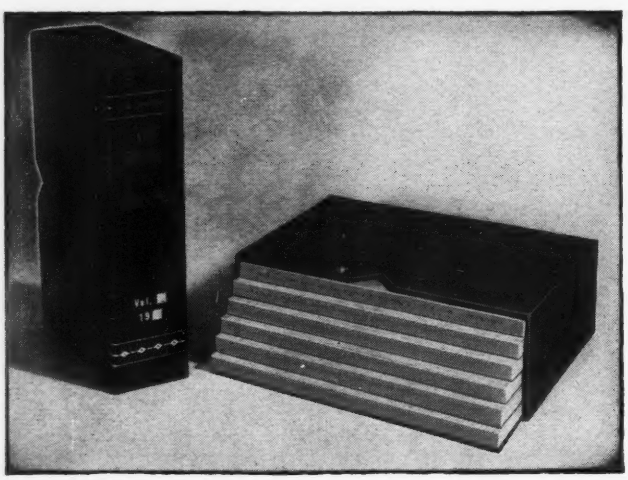

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■ helps the cardiac or hypertensive patient slow down to the safer pace you recommend ■ controls the agitation and tension that aggravate his condition[1,2] ■ calms the patient and helps him get to sleep more easily ■ relatively free of side effects[1-3] ■ low in cost, particularly when long-term or adjunctive therapy is indicated

dosage: Total daily dosage may range from as low as 40 mg. (one 20 mg. tablet twice daily) to as high as 80 mg. daily. **Generally, the most effective dosage is 20 mg. t.i.d.** In those patients who have difficulty sleeping, the last tablet should be taken one hour before retiring. **supply:** TINDAL Tablets, 20 mg., bottles of 100 and 1000.

references: (1) Hirshleifer, I.: Adjunctive therapy in cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961. (2) Frohman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, **ibid.** (3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, **ibid.**

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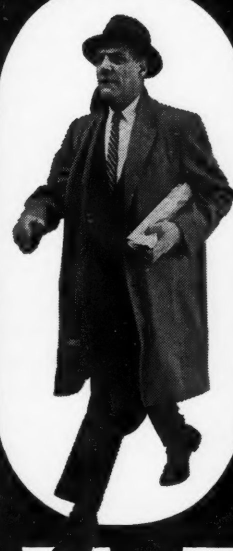
FOR YOUR CARDIOVASCULAR PATIENT...WHEN YOU HAVE TO SAY

SLOW DOWN



No. 4 **of a series reporting on Endo Laboratories' Anticoagulant Survey**

Nationwide Survey Explores Current Use of Anticoagulants in Venous Thrombosis and Arterial Embolism

Immediate institution of anticoagulant therapy is now accepted by most physicians for the control of thrombotic disease affecting the veins. By inhibiting further propagation of an already formed thrombus, anticoagulation helps to reduce disability and prevent new and potentially fatal thromboembolic episodes.

These concepts of treatment are supported by the responses of 10,016 physicians who contributed their experience to Endo Laboratories' *Anticoagulant Survey* completed earlier this year. Analysis of the data showed that the use of anticoagulation was more often therapeutic than prophylactic.

Indication	All Anticoagulants: Therapeutically	All Anticoagulants: Prophylactically
Acute Thrombophlebitis	69.9%	18.5%
Recurrent Chronic Thrombophlebitis	54.8%	30.4%
Deep Venous Thrombosis	62.5%	21.2%
Phlebothrombosis	53.7%	20.0%
Arterial Embolism	60.9%	22.5%
Pulmonary Embolism	68.7%	25.1%

Figures refer to percentage of physicians prescribing oral anticoagulants

Specialists Lead in Therapeutic Application of Anticoagulants

The chart below indicates the use of Coumadin—the most widely prescribed oral anticoagulant among both general practitioners and specialists—in the foregoing conditions. Proportionately, anticoagulation with this agent was employed to a greater extent by internists and cardiologists than by the responding general practitioners. For example, 76.9% of 2,626 specialists prescribing Coumadin most often used the drug therapeutically in *deep venous thrombosis* with its associated danger of pulmonary embolism, compared to 56.2% of 3,092 general practitioners using Coumadin.

Indication	General Practitioners	Specialists
Acute Thrombophlebitis	65.6%	82.5%
Recurrent Chronic Thrombophlebitis	48.7%	67.9%
Deep Venous Thrombosis	56.2%	76.9%
Phlebothrombosis	48.2%	66.9%
Arterial Embolism	53.2%	75.3%
Pulmonary Embolism	61.3%	84.2%

Figures refer to percentage of physicians prescribing Coumadin® therapeutically

Although anticoagulants were used less often for prophylaxis than for therapy, it is noteworthy that in *recurrent chronic thrombophlebitis*, for example, as high as 38.2% of the reporting specialists and 26.5% of the general practitioners employed Coumadin prophylactically.

Anticoagulants Minimize Mortality Due to Pulmonary Embolism

Through the use of anticoagulants in venous thrombosis, mortality from subsequent pulmonary emboli "can be reduced from 18 per cent to less than 1 per cent."[1] Anticoagulation is an established measure of choice in the management of thrombophlebitis.[1-3] Mead and Wright[1] suggest that ligation be reserved for those cases in which anticoagulation fails to stop the thrombophlebitic process, since the late effects of ligation are often undesirable.

Selection of Coumadin as the oral anticoagulant of choice offers the advantages of rapid, consistent effect and "predictability of dosage."[3] For routine postoperative protection against pulmonary embolism, Coumadin "appears to be the most predictable and consequently the safest and most effective anticoagulant drug..."[4] Since Coumadin, the first clinically established warfarin sodium, is presented in parenteral dosage forms for I.V. or I.M. administration as well as in a broad range of tablet potencies, it is the most versatile anticoagulant in hospital and office practice.

1. Mead, A. W., and Wright, I. S.: M. Clin. North America 45:907, 1961. 2. Olwin, J. H., and Koppel, J. L.: S. Clin. North America 39:193, 1959. 3. Kirtland, H. B., Jr., et al.: California Med. 92:409, 1960. 4. Belding, H. H.: West. J. Surg. 68:84, 1960.

Coumadin (warfarin sodium) is manufactured under license from the Wisconsin Alumni Research Foundation, and is supplied as scored tablets of 2 mg., lavender; 2½ mg., orange; 5 mg., peach; 7½ mg., yellow; 10 mg., white; and 25 mg., red, as well as in 50 mg. and 75 mg. single-injection units.

Another professional service of Endo Laboratories—makers of

COUMADIN®

the proven anticoagulant for long-term maintenance

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

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to prevent pain and anxiety in angina

For your angina patients, EQUANITRATE helps control pain and angina-triggering anxiety. EQUANITRATE reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerine dependence. Russek† reports "The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE] in the patients studied."

For further information on the limitations, administration, and prescribing of EQUANITRATE, see descriptive literature or current direction circular.

†Russek, H.I.: Am J. Cardiol. *3*:547 (April) 1959.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

Wyeth Laboratories Philadelphia 1, Pa.

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Equanitrate®

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

Here are three good reasons why you should write "Raudixin" in the treatment of high blood pressure:

1. Biological assay measures the ability to produce ptosis in the mouse in comparison with a reference standard.

2. Biological assay measures the ability to counteract the pressor effect of standard doses of epinephrine in the dog.

3. Every Raudixin tablet to reach your patient meets the high Squibb standards for effectiveness, potency and uniformity.

For full information, see your Squibb Product Reference or Product Brief.

Raudixin

Squibb Standardized Whole Root Rauwolfia Serpentina

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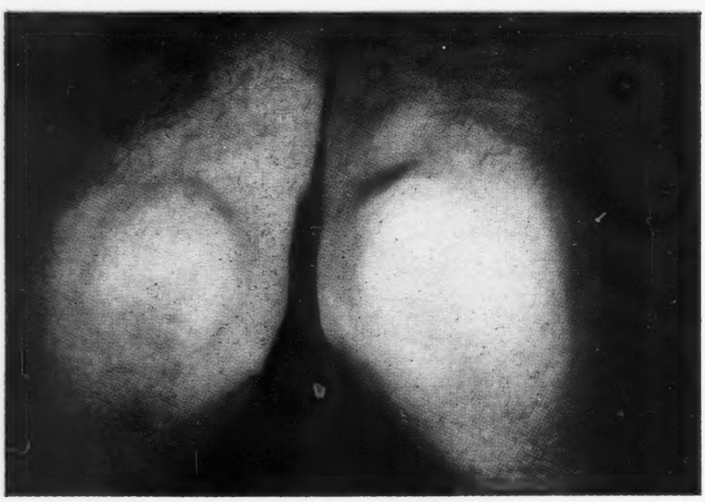
VISIBLE EVIDENCE...

Nicalex reduces abnormal tissue and serum cholesterol

August 7, 1959: Patient with Familial Hypercholesteremia and Xanthoma Tuberosum of both elbows for 14 years. Total serum cholesterol: 720 mg.%. Beta-lipoprotein cholesterol: 300 mg.%.[1,2] NICALEX, 2 tablets t.i.d. prescribed. No other medication.



February 21, 1961: Clinically the xanthomata have disappeared. No palpable deposits. The areas are soft and not elevated. Total serum cholesterol: 164 mg.%. Beta-lipoprotein cholesterol: 93 mg.%.[1,2] NICALEX continued, 2 tablets t.i.d. No side effects observed.

This case demonstrates the dramatic clinical role of NICALEX in reducing abnormal cholesterol levels in serum and tissue. According to one recent study "... the rapid visible regression of these lipid deposits [xanthomata] ... following reduction of serum cholesterol levels, provides the best direct clinical evidence we may ever have for the resorption of atherosclerotic-like lipid deposits."[3]

Sustained cholesterol-lowering and antilipemic effects—NICALEX, a newly synthesized salt of nicotinic acid, lowers serum cholesterol as well as phospholipid and triglyceride levels effectively and rapidly. Further, because it is well tolerated, NICALEX can maintain lowered cholesterol and total lipid levels with or without adjunctive dietary restrictions.

Side effects reduced—NICALEX is hydrolyzed uniformly in the gastrointestinal tract into free nicotinic acid, with nascent aluminum hydroxide splitting off to provide effective buffering action. With NICALEX there is a reduced incidence of flushing and gastrointestinal upset. Thus, NICALEX provides the therapeutic effects of nicotinic acid, "...the most uniformly effective agent..."[4] in the treatment of hypercholesteremia, with a high degree of patient acceptance and cooperation.

Dosage: 2 to 4 tablets t.i.d., with or after meals. Each tablet contains Aluminum Nicotinate Walker 625 mg., a complex consisting of (approx.): Aluminum Nicotinate 345 mg.; Nicotinic Acid 200 mg.; and Aluminum Hydroxide 80 mg. Equivalent in activity to 500 mg. Nicotinic Acid.

Supplied: Bottles of 100 and 1,000 tablets.

Caution: Federal law prohibits dispensing without prescription.

References: 1. Parsons, W. B., Jr.: Arch. Int. Med. *107*:71, 1961. 2. Parsons, W. B., Jr.: Personal communication. 3. Taylor, C. B., *et al.*: Illinois M.J. *119*:80, 1961. 4. Christensen, N. A., *et al.*: J.A.M.A. *177*:546, 1961.

NICALEX

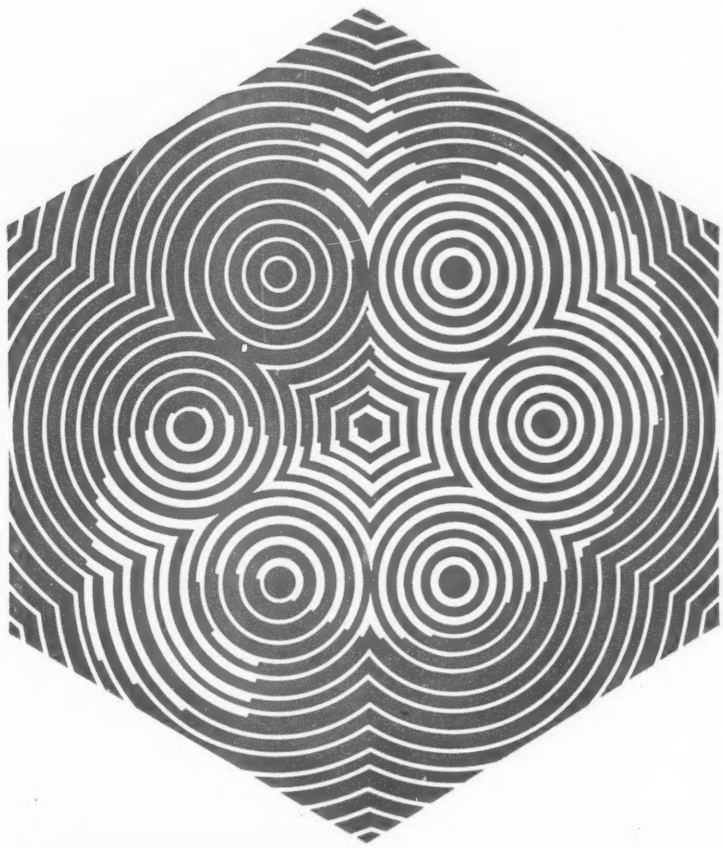
TABLETS Aluminum Nicotinate Walker*

WALKER LABORATORIES, INC., Mount Vernon, N. Y.

*U. S. PAT. 2,970,082

"UPSET STOMACH" ON DIGITALIS 52-year old male had rheumatic heart disease, cardiomegaly Grade II, auricular fibrillation, mitral stenosis, mitral insufficiency, and was in class III-C. For 17 months he had been in failure. Three grains of digitalis daily were required for effective maintenance therapy. When the patient began to complain of frequent "upset stomach", he was placed on digitoxin, with an alternating 0.1 and 0.2 daily maintenance dose. Nausea became very severe after two months, and digitoxin was decreased to 0.1 mg. daily. Congestive failure increased and rehospitalization was necessary. Patient was given GITALIGIN, 0.5 mg. q.i.d. for two days, then 1.5 mg. daily for six weeks, followed by 1.0 mg. per day with 1.5 mg. every third day. Failure was effectively controlled without toxicity.[1]

"DIGITALIS TOXICITY IS SEEN WITH INCREASING FREQUENCY TODAY..."[2]



for maximal digitalis activity with minimal toxicity

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"...patients who became toxic very readily with other agents could later be satisfactorily digitalized with gitalin (GITALIGIN)."[2]
Wider margin of safety—frequently effective in patients refractory to other digitalis glycosides • broader clinical utility—therapeutic dose only ⅓ the toxic dose • faster rate of elimination than digitoxin or digitalis leaf. □ Supplied: 0.5 mg. scored tablets—bottles of 30 and 100.

1. Dimitroff, S. P. et al.: Ann. Int. Med. 39:1189, 1953. 2. Pastor, B. H.: GP 22:85, 1960.

†amorphous gitalin, White   White   WHITE LABORATORIES, INC. • Kenilworth, New Jersey

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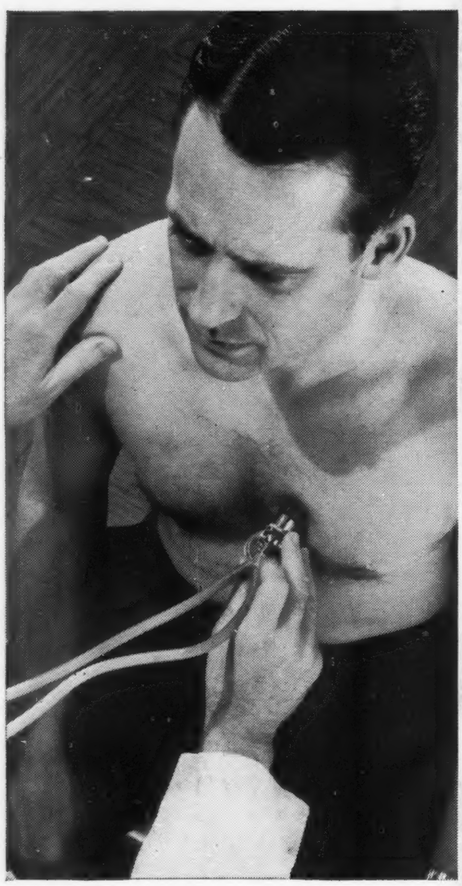

Since initial digitalization and maintenance dosage must be carefully individualized, Crystodigin fulfills the important requirements of a preferred digitalis. Crystodigin is a crystalline-pure, uniformly potent single glycoside that is completely absorbed in the gastro-intestinal tract. With Crystodigin, the maximum therapeutic effect can be readily obtained by dosage titration in increments as small as 0.025 mg.

Available in scored tablets of 0.05 mg. (orange), 0.1 mg. (pink), 0.15 mg. (yellow), and 0.2 mg. (white); and in 1-cc. and 10-cc. ampoules, 0.2 mg. per cc.

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